



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 66

Alan R. Katritzky

Advances in

# Heterocyclic Chemistry

Volume 66

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Advances in

# HETEROCYCLIC CHEMISTRY

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**Volume 66**



ACADEMIC PRESS

San Diego London Boston New York  
Sydney Tokyo Toronto

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**Academic Press, Inc.**

A Division of Harcourt Brace & Company  
525 B Street, Suite 1900, San Diego, California 92101-4495

*United Kingdom Edition published by*  
Academic Press Limited  
24-28 Oval Road, London NW1 7DX

International Standard Serial Number: 0065-2725

International Standard Book Number: 0-12-020766-4

PRINTED IN THE UNITED STATES OF AMERICA

96 97 98 99 00 01 BB 9 8 7 6 5 4 3 2 1

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## Preface

Volume 66 of our serial consists of five chapters. Ring-chain tautomerism was covered in an authoritative monograph by Valters and Flitch, which appeared in 1985. Now Professor Valters (Latvia), together with Professor Fülöp and Dr. Korbonits (Hungary), has updated this monograph in two chapters for our serial. The first of these has already appeared in Volume 64. The second, covering intramolecular reversible addition reactions to  $C=N$  and other groups, constitutes the first chapter of this volume.

The palladium-allylation of ambident aromatic heterocycles is covered by Professor Moreno-Mañas and Dr. Pleixats (Barcelona, Spain) in the second chapter of this volume. The preference for carbon versus oxygen, nitrogen, and sulfur allylation is discussed from the diverse viewpoints of regioselectivity, kinetic versus thermodynamic control, mechanisms, stereochemistry, and synthetic targets in the first general survey of this topic.

The third chapter in the present volume is by Drs. Ryabukhin, Korzhavina, and Suzdalev (Rostov University, Russia), who have provided the first specialized review of 1,3-thiazin-4-ones. Professor Varvounis and Dr. Giannopoulos (Ioannina, Greece) cover recent developments in the synthesis, chemistry, and biological properties of the thienopyrimidines in the fourth chapter of this volume.

*Advances in Heterocyclic Chemistry*, Volume 64 also contained the first section of a review by Dr. G. Fischer (Leipzig, Germany) on tropones, tropolones, and tropylium salts with fused heterocyclic rings. This overview has now been completed in the fifth and final chapter of the present volume, which covers the structure, reactivity, and applications of these compounds.

ALAN R. KATRITZKY

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# Recent Developments in Ring-Chain Tautomerism

## II. Intramolecular Reversible Addition Reactions to the C=N, C≡N, C=C, and C≡C Groups

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## I. Introduction

This work is the second part of the review article "Recent Developments in Ring-Chain Tautomerism" [95AHC(64)251]. In Part I of this article the present authors updated the book (I)<sup>1</sup> by R. Valters and W. Flitsch and reviewed intramolecular reversible addition reactions to the C=O group. In Part II, intramolecular reversible addition reactions to the C=N group and other groups are discussed. The first sections offer an introduction to and general considerations of the ring-chain tautomeric process, while the last section presents general conclusions and prospects.

## II. Intramolecular Reversible Addition Reactions to the C=N Group

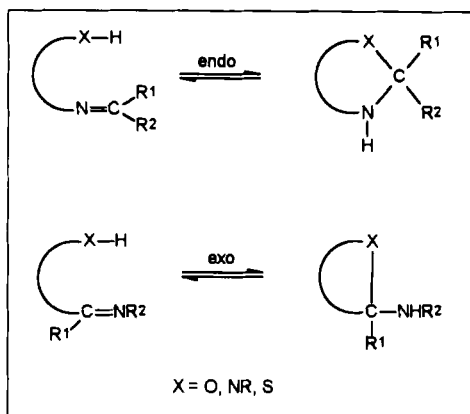
Despite the lower reactivity of the azomethine group as compared with the carbonyl group, intramolecular reversible nucleophilic additions of OH, NH, or SH groups to the C=N bond often proceed. The intramolecular addition of nucleophilic groups to the C=N bond can occur along two pathways (*endo* and *exo*), depending on the orientation of the azomethine group in the molecule.

### A. ADDITION OF AN OH GROUP

#### 1. *N*-Hydroxyalkyl and *N*-Hydroxyaryl Imines

Investigations of ring-chain tautomerism in this group of organic compounds have undergone extensive development during the past decade. A

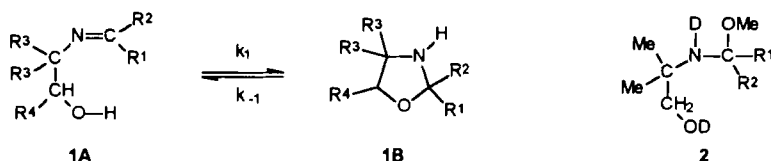
<sup>1</sup> Here and throughout the chapter, "book (I)" refers to the book by R. E. Valters and W. Flitsch, *Ring-Chain Tautomerism* (A. R. Katritzky, ed.), Plenum Press, New York and London, 1985; and references such as "(I-50)" indicate the page numbers therein.



new approach has been proposed [87JOC3821, 87T1863; 94ACH(131)697] for a quantitative characterization of the influence of a connecting-link structure on ring-chain equilibria of this type.

Quantitative measurements of the equilibrium  $\mathbf{1A} \rightleftharpoons \mathbf{1B}$  have been carried out by means of  $^1\text{H}$ -NMR spectroscopy [82MI1; 85T5919; 86JST(147)105; 91ZPK1052], with approximate measurements in the gas phase by mass spectrometry [90T3683; 91OMS(36)438; 93RCM465]. The possibility of using  $^{15}\text{N}$ -NMR spectroscopy for the investigation of such systems has been demonstrated [the  $^{15}\text{N}$  signal for  $\mathbf{1A}$  ( $\text{R}^1 = \text{Me}$ ;  $\text{R}^2 = \text{Me, Et}$ ;  $\text{R}^3 = \text{R}^4 = \text{H}$ ) appears at 69–76 ppm; and that for  $\mathbf{1B}$  appears at 305–316 ppm] (83HCA1537). For determination of the solid-state structure of these compounds, solid-state NMR spectroscopy (CP/MAS technique) has been utilized (85T5919; 92T4979), in addition to IR spectroscopy (91ZPK1052).

According to Baldwin's rules [76JCS(CC)234; 92MI1; 93ACR476], the cyclization  $\mathbf{1A} \rightarrow \mathbf{1B}$ , as a 5-*endo-trig* process, is disallowed. But despite these rules, the transformation  $\mathbf{1A} \rightarrow \mathbf{1B}$  is rather fast. Thus, the rate constant of the monomolecular cyclization of iminoalcohol  $\mathbf{1A}$  ( $\text{R}^1 = \text{H}$ ;  $\text{R}^2 = \text{Me}$ ;  $\text{R}^3 = \text{Ph}$ ), for example, has been estimated as  $k_1 > 0.06 \text{ s}^{-1}$



(85T5919). The mechanism of ring closure in  $\text{CD}_3\text{OD}$  has been presumed to involve intermediate **2**, the further cyclization of which proceeds via the allowed 5-*exo-tet* process (85T537; 85T5919). However, this explanation is useless for the rapid transformation **1A**  $\rightarrow$  **1B** in nonhydroxylic solvents.

By means of  $^1\text{H}$ -NMR spectroscopy (82MI1), the equilibrium constants for **1A**  $\rightleftharpoons$  **1B** (for  $\text{R}^1\text{--R}^4$ , see Table I) in the form of neat liquids and solutions have been measured at different temperatures, and the thermodynamic parameters  $\Delta H^\circ$  and  $\Delta S^\circ$  have been calculated. As shown in Table I, an increase in the number of substituents in the chain displaces the equilibrium in favor of the cyclic tautomer. The increasing steric demands of the substituent  $\text{R}^2$  (when  $\text{R}^1 = \text{Me}$ ) in the series  $\text{Et} < i\text{-Pr} < t\text{-Bu}$  destabilize the cyclic tautomer. However, the 2,2-dimethyl derivative **1** ( $\text{R}^1 = \text{R}^2 = \text{Me}$ ) does not obey the general regularity and exhibits a lower  $K_T$  than might be expected. On passing from the neat liquids to solutions, the equilibrium constants increase; this increase may be attributable to disruption of the intermolecular hydrogen bonds  $\text{OH}\cdots\text{N}$  stabilizing the open-chain tautomers **1A**. This effect causes an increase of *ca.* 0.96 kcal/mol in  $\Delta H^\circ$ . For the same reason, dilution of the solutions stabilizes the cyclic tautomer (91ZPK1052).

A good linear correlation was obtained (82MI1) between the free enthalpy differences for the open-chain and cyclic tautomers of **1** ( $\text{R}^1 = \text{Me}$ ;  $\text{R}^2 = \text{alkyl}$ ) and the constants  $\sigma^*$  and  $E_s$  of substituent  $\text{R}^2$ :

$$-\Delta H^\circ = (1.53 \pm 0.15) + (8.30 \pm 1.75)\sigma^* - (2.06 \pm 0.32)E_s \text{ kcal/mol};$$

$$r = 0.991; \quad s = 0.15$$

and for **1** ( $\text{R}^1 = \text{R}^4 = \text{Me}$ ;  $\text{R}^2 = \text{alkyl}$ ):

$$-\Delta H^\circ = (2.92 \pm 0.1) - (6.44 \pm 1.15)\sigma^* + (0.55 \pm 0.21)E_s \text{ kcal/mol};$$

$$r = 0.993; \quad s = 0.10.$$

In the series of *N*-(2-hydroxyethyl)imines of benzaldehyde and its *p*-substituted derivatives **1** ( $\text{R}^1 = \text{H}$ ;  $\text{R}^2 = 4\text{-XC}_6\text{H}_4$ ,  $\text{X} = \text{H}$ ,  $\text{NMe}_2$ ,  $\text{NHCOOR}$ ,  $\text{NO}_2$ ), which do not contain alkyl substituents in the chain between the interacting groups ( $\text{R}^3 = \text{R}^4 = \text{H}$ ), the presence of cyclic tautomer **1B** was detected in  $\text{CDCl}_3$  solution by means of  $^1\text{H}$ -NMR only for **1** ( $\text{X} = \text{NO}_2$ ), with  $K_T = 0.18$  (81PJC2025) and  $K_T = 0.169$  (91ZPK1052). A very small amount of **1B** (*ca.* 3%,  $K_T = 0.036$ ) was detected at equilibrium (91ZPK1052) for the unsubstituted benzaldehyde derivative **1** ( $\text{X} = \text{H}$ ). An intercept value  $\log(K_T)_0 = -1.10$  ( $K_T = 0.079$ ) was obtained (93JOC1967) in the correlation analysis of the derivatives **3** ( $\text{R} = \text{H}$ ) in this series.

TABLE I  
RING-CHAIN EQUILIBRIUM **1A**  $\rightleftharpoons$  **1B** ( $R^1 = \text{Me}$ ) CONSTANTS OF ALKYL-SUBSTITUTED  
1,3-OXAZOLIDINES AND THERMODYNAMIC PARAMETERS OF EQUILIBRIUM<sup>a</sup>

R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	$K_T$			$-\Delta H^\circ(\text{kcal/mol})$			$-\Delta S^\circ(\text{cal/mol K})$		
			Neat liquid	CCl <sub>4</sub>	C <sub>6</sub> H <sub>6</sub>	Neat liquid	CCl <sub>4</sub>	C <sub>6</sub> H <sub>6</sub>	Neat liquid	CCl <sub>4</sub>	C <sub>6</sub> H <sub>6</sub>
Me	H	H	0.77	1.64	2.38	1.62	2.15	—	5.25	5.73	—
Et	H	H	1.85	7.69	4.0	1.07	2.36	3.58	2.08	3.10	7.88
<i>i</i> -Pr	H	H	—	4.0	2.56	0.96	1.89	2.36	3.10	2.96	5.25
<i>t</i> -Bu	H	H	0.5	2.63	1.89	2.36	3.34	1.93	8.12	8.36	4.53
Me	H	Me	1.82	5.0	4.17	2.94	3.82	2.41	7.64	8.12	1.85
Et	H	Me	5.26	11.1	3.45	3.34	1.89	—	7.40	7.88	—
<i>i</i> -Pr	H	Me	2.78	3.45	5.0	3.82	—	2.87	8.60	—	5.73
<i>t</i> -Bu	H	Me	2.44	3.33	3.13	4.06	—	—	10.0	—	—
Et	Me	H	2.63	12.5	10.0	—	—	—	—	—	—
<i>i</i> -Pr	Me	H	2.56	2.44	2.13	1.98	2.10	1.12	4.06	4.54	1.86

<sup>a</sup> Data from Pihlaja and Aaljoki (82MI1). Determined by <sup>1</sup>H-NMR. The  $K_T$  data in the table were determined at 45°C. For the calculation of  $\Delta H^\circ$  and  $\Delta S^\circ$ ,  $K_T$  was measured at 10, 33.5, 45, 60, 75, 100, and 125°C—the last two for the neat liquids only. The concentration of the solutions was 20% v/v.



A good correlation between  $\log K_T$  and the Hammett–Brown constant  $\sigma^+$  of substituent X was obtained in the series **3–11** (see Table II and references therein):

$$\log K_T = \log(K_T)_0 + \rho\sigma^+.$$

Furthermore, the constant  $c$  has been introduced (87JOC3821), which allows a quantitative comparison of the influence of the connecting link structure on the ring–chain equilibrium state:

$$c = \log(K_T)_Y^Y - \log(K_T)_0^{\text{ref}},$$

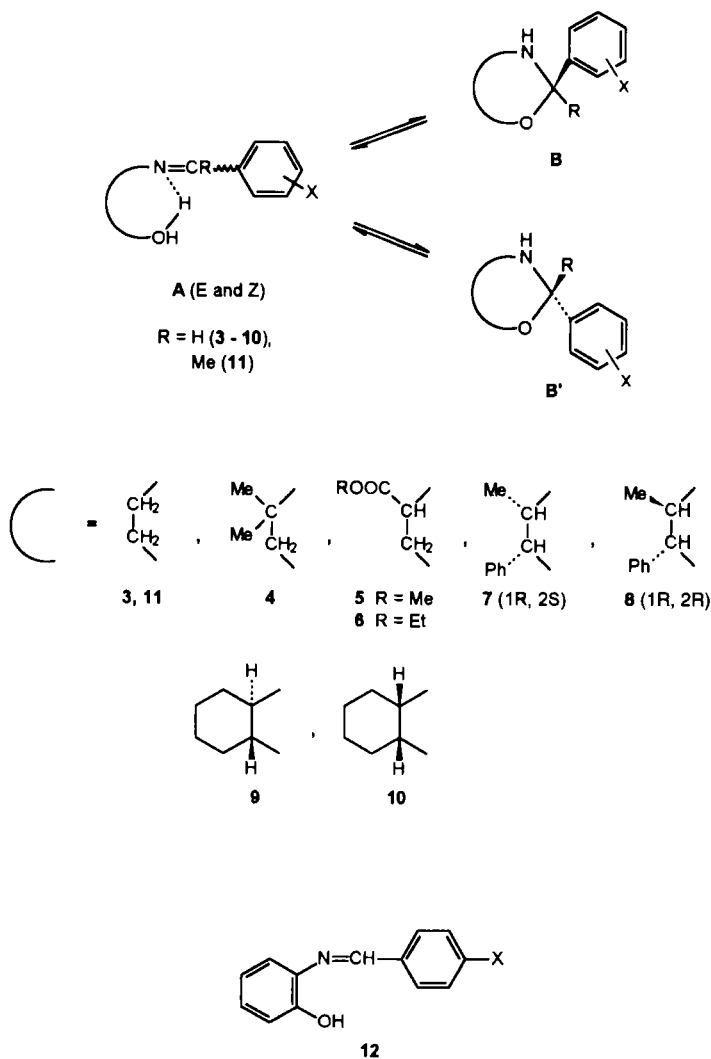
where  $(K_T)_Y^Y$  is the intercept value of some system Y (one of **4–11**; see Table II) whose structural influence remains to be characterized, and  $(K_T)_0^{\text{ref}}$  is the intercept of the reference system—i.e., the unsubstituted ethylene (**3**) or trimethylene (**13**) connecting link.

It is obvious from Table II that dimethyl substitution in the connecting link ( $c = 1.45$  for **4**) strongly stabilizes the cyclic tautomer. The Schiff bases **7** and **8** [for the structure of the compounds in the solid state, see (92T4979)], obtained in the reactions of ( $\pm$ )-norephedrine (only the **1R,2S** enantiomer is shown) and (**1R,2R**)-norpseudoephedrine with eleven *m*- and *p*-substituted benzaldehydes, exhibit three-component tautomeric equilibria  $\mathbf{B} \rightleftharpoons \mathbf{A} \rightleftharpoons$

TABLE II  
INFLUENCE OF THE CONNECTING-LINK STRUCTURE ON RING-CHAIN  
EQUILIBRIUM OF 2-ARYLOXAZOLIDINES  
LINEAR REGRESSION ANALYSIS DATA<sup>a</sup>

Series	Type of tautomerism	$c$	$\log(K_T)_0$	$\rho$	$r$	$s^b$	$n$	References
<b>3</b>	r-o	0	-1.10	0.60	0.989	0.04	7	<sup>c</sup>
<b>4</b>	r-o	1.45	0.35	0.55	0.998	0.02	7	<sup>c</sup>
<b>4</b>	r <sup>1</sup> -o-r <sup>2</sup>	1.30	0.20	0.47	0.993	0.02	11	<sup>d</sup>
<b>5</b>	r <sup>1</sup> -o-r <sup>2</sup>	1.01	-0.09	0.61	0.991	0.04	7	<sup>f</sup>
<b>6</b>	r <sup>1</sup> -o-r <sup>2</sup>	1.10	0.00	0.60	0.993	0.01	7	<sup>f</sup>
<b>7</b>	r <sup>1</sup> -o-r <sup>2</sup>	0.84	-0.36	0.54	—	0.02	11	<sup>e</sup>
<b>8</b>	r <sup>1</sup> -o-r <sup>2</sup>	1.44	0.34	0.53	—	0.02	11	<sup>e</sup>
<b>10</b>	r <sup>1</sup> -o-r <sup>2</sup>	-0.24	-1.34	0.56	0.999	0.00	7	<sup>c</sup>
<b>11</b>	r <sup>E</sup> -o-r <sup>Z</sup>	1.37	0.27	0.57	0.994	0.04	5	<sup>c,g</sup>
<b>11</b>	r <sup>E</sup> -o-r <sup>Z</sup>	1.29	0.19	0.47	0.993	0.03	5	<sup>c,g</sup>

<sup>a</sup> Determined by <sup>1</sup>H-NMR (400 MHz) in CDCl<sub>3</sub> at 20°C.  $K_T = [\mathbf{B} + \mathbf{B}']/[\mathbf{A}]$ . The compounds in series **9** did not exhibit any detectable amount of the cyclic tautomer **9B**; <0.01% of **9B** can be present even with X = NO<sub>2</sub>. <sup>b</sup> Standard error of slope ( $\rho$ ). <sup>c</sup> Data from Fülöp *et al.* (93JOC1967). <sup>d</sup> Data (at 35°C) from Alva Astudillo *et al.* (85T5919). <sup>e</sup> Data from Fülöp *et al.* (89T4317). <sup>f</sup> Data from Fülöp and Pihlaja (93T6701). <sup>g</sup> The first line refers to  $K = [\text{ring}]/[\text{chain}(E)]$  and the second line to  $K = [\text{ring}]/[\text{chain}(E + Z)]$ .



**B'** in  $\text{CDCl}_3$  solution. These equilibria are attained rather slowly (in 4–48 hours), depending on the substituent X: relatively quickly with  $\text{X} = \text{NMe}_2$ , but slowly with  $\text{X} = \text{NO}_2$  (89T4317). From a comparison of the  $c$  values (Table II), it is apparent that the cyclic tautomers of the *threo*-alcohol derivatives **8** are more stable than those of the *erythro* series **7**. The stereoselectivity of the ring closure, characterized by the epimeric ratio  $[\mathbf{B}]/[\mathbf{B}']$ , also exhibits a linear correlation with the constants  $\sigma^+$  of the substituents

X in both series [see also (86JST(147)105)]. The stability of the cyclic tautomer is decreased for the *cis*-2-aminocyclohexanol derivatives **10** ( $c = -0.24$ ). Moreover, in the series of the *trans*-2-aminocyclohexanol derivatives **9**, the cyclic tautomer could not be detected at all (93JOC1967). The introduction of a methyl group at position 2 of the oxazolidine ring strongly stabilizes the cyclic tautomer ( $c = 1.29$  for **11**).

Table II reveals that the coefficients  $\rho$ , which characterize the sensitivity of the tautomeric system to the influence of the electronic effects of substituent X, are rather similar for all systems investigated.

For series **7** and **8** in the gas phase, mass spectrometry yielded coefficients  $\rho$  close to those of nonpolar solutions (90T3683), but the intercepts  $\log(K_T)_0$  differ significantly, showing the equilibrium shift in favor of the open-chain tautomer. Thus, for **7**,  $\log(K_T)_0 = 0.14$ ,  $\rho = 0.58$ , and  $r = 0.980$ ; **8**,  $\log(K_T)_0 = 0.30$ ,  $\rho = 0.55$ , and  $r = 0.993$  (for 14-eV ionizing electrons and an ion source temperature of 170°C). Neither the ion source temperature nor the energy of the ionizing electrons has any great influence on the  $\rho$  values. Instead, the intercept values  $\log(K_T)_0$ , characterizing the state of the ring-chain equilibrium in the gas phase, vary considerably with the mass-spectrometric experimental conditions. The higher the ion source temperature and/or the greater the ionizing energy, the more favorable is the formation of open-chain tautomer daughter ions in the gas phase (93MI1; 93RCM465).

Solid-state  $^{13}\text{C}$ -NMR and IR spectroscopy (85T5919) demonstrated that the oxazolidines **1** ( $\text{R}^1 = \text{H, Me}$ ;  $\text{R}^2 = \text{XC}_6\text{H}_4$ ;  $\text{R}^3 = \text{Me}$ ;  $\text{R}^4 = \text{H}$ ) exist in the solid state or the neat liquid only in the cyclic form. The correlation parameters for the equilibrium system **1A**  $\rightleftharpoons$  **1B** ( $\text{R}^1 = \text{R}^4 = \text{H}$ ;  $\text{R}^2 = \text{XC}_6\text{H}_4$ ; X = 4-Me<sub>2</sub>N, 4-MeO, 4-Me, 3-Me, H, 4-F, 4-Cl, 3-F, 3-Cl, 3-Br, 3-NO<sub>2</sub>, 4-NO<sub>2</sub>;  $\text{R}^3 = \text{Me}$ ) were determined in various solvents. From the data in Table III, it is obvious that the correlation is better with  $\sigma^+$  than with  $\sigma$ . The dependence of  $\rho$  on the solvent polarity is rather small, but the equilibrium constants vary considerably with the change of solvent (93JOC1967, 93T6701). Increasing solvent proton-accepting ability stabilizes the open-chain tautomer.

The preferences of nineteen oxazolidines **7** and **8** and tetrahydrooxazines **13** and **20–22** for the ring or chain tautomeric form were studied by means of 500-MHz solid-state NMR. The chain form is preferred in the solid state when <80% of the ring tautomer is observed in CDCl<sub>3</sub> solution. Exclusively the ring form was found in the solid state only for those derivatives exhibiting a 93% preference for the ring tautomer in CDCl<sub>3</sub> solution (92T4979).

The reaction products of 2-aminophenol with substituted benzaldehydes in CDCl<sub>3</sub> and CF<sub>3</sub>COOH solutions possess the open-chain structure **12** (X = Me<sub>2</sub>N, MeO, Me, H, Cl, NO<sub>2</sub>) (85T5919; 90T6545).

TABLE III  
INFLUENCE OF SOLVENTS ON EQUILIBRIUM **1A**  $\rightleftharpoons$  **1B** ( $R^1 = R^4 = H$ ;  
 $R^2 = XC_6H_4$ ;  $R^3 = Me$ ) CONSTANTS AND CORRELATION  
ANALYSIS COEFFICIENTS<sup>a</sup>

Solvent	$(K_T)_0$ ( $X = H$ )	$\sigma$		$\sigma^+$	
		$\rho$	$r$	$\rho$	$r$
CCl <sub>4</sub>	2.26	0.63	0.968	0.50	0.988
CS <sub>2</sub>	1.86	0.83	0.976	0.50	0.992
CHCl=CCl <sub>2</sub>	1.95	0.77	0.923	0.52	0.975
CDCl <sub>3</sub>	1.59	0.69	0.952	0.47	0.993
(CD <sub>3</sub> ) <sub>2</sub> CO	0.45	0.61	0.922	0.42	0.980
CD <sub>3</sub> CN	0.67	0.56	0.919	0.39	0.978
CD <sub>3</sub> OD	0.39	0.60	0.939	0.41	0.989
(CD <sub>3</sub> ) <sub>2</sub> SO <sup>b</sup>	0.11	0.68	0.913	0.48	0.877

<sup>a</sup> Data from Alva Astudillo *et al.* (85T5919).  $K_T$  determined by <sup>1</sup>H-NMR at 35°C,  $n = 10$ . <sup>b</sup> The inaccuracy of the correlation is caused by a strong predominance of the open-chain tautomer in (CD<sub>3</sub>)<sub>2</sub>SO solution.

Fülöp and co-workers have measured (<sup>1</sup>H-NMR, 400 MHz) the ring-chain equilibrium constants of a large number of aryl group-substituted 2-aryltetrahydro-2*H*-1,3-oxazines **13–15** and their fused analogs **16–29** in CDCl<sub>3</sub>, determined the correlation parameters, and calculated the cyclic tautomer stability constants, thereby allowing a quantitative comparison of the dependence of the equilibrium state on the connecting-link structure (see Table IV). The investigation of tetrahydrooxazines **14** and **15** bearing the aryl group (YC<sub>6</sub>H<sub>4</sub>) at position 4 or 6 of the oxazine ring showed (93T2115) that the substituent Y does not exert any observable influence on the equilibrium state. However, the presence of the aryl group itself stabilizes the cyclic tautomer, more significantly at position 4 (**15**,  $c = 0.56$ ) than at position 6 (**14**,  $c = 0.14$ ). For the systems **16** and **17** containing the 1,3-oxazine ring *cis*-fused with the cyclopentane ring, the cyclic tautomers are more stable ( $c > 0$ ) than the reference system **13**; but *trans* fusion of the rings in the systems **18** and **19** leads to a significant destabilization of the cyclic tautomer ( $c < 0$ ). In contrast, cyclohexane-fused oxazines **22** and **23** with *trans*-fused rings have larger stability constants than those of the *cis*-fused systems **20** and **21**. The same regularity was observed for the cyclohexene-fused derivatives **24** and **25**. In the case of rigid *diexo*- and especially *diendo*-norbornane-fused derivatives **26** and **27**, the cyclic tautomers have very low stability relative to the reference system **13**. The lower stability of the cyclic tautomer in the benzoxazine system **29** may be attrib-

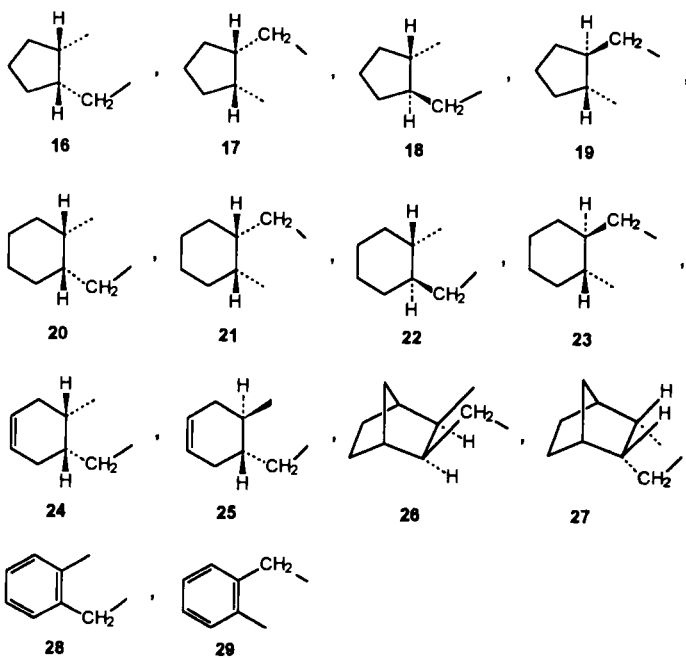
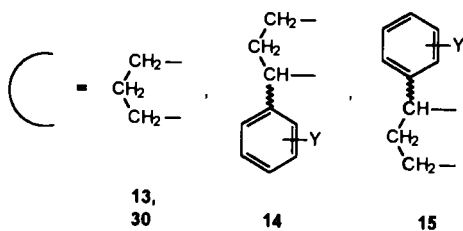
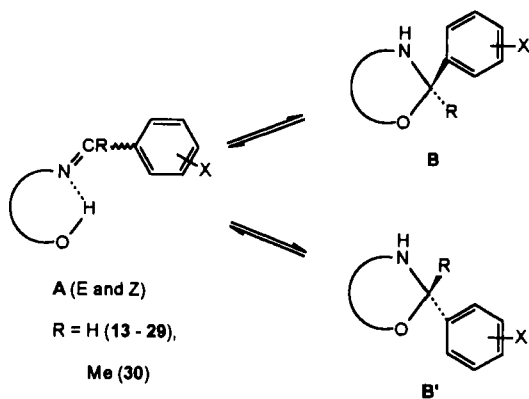


TABLE IV  
INFLUENCE OF CONNECTING-LINK STRUCTURE ON RING-CHAIN EQUILIBRIUM OF  
2-ARYLTETRAHYDRO-2H-1,3-OXAZINES (13-30) LINEAR REGRESSION ANALYSIS DATA<sup>a</sup>

Series	<i>c</i>	log( <i>K</i> <sub>T</sub> ) <sub>0</sub>	<i>ρ</i>	<i>r</i>	<i>s</i> <sup>b</sup>	<i>n</i> <sup>c</sup>	References
13	0	-0.15	0.74	0.984	0.06	7	<sup>d</sup>
14 <sup>e</sup>	0.14	-0.01	0.81	0.997	0.03	6	<sup>f</sup>
15 <sup>e</sup>	0.56	0.41	0.71	0.995	0.04	6	<sup>f</sup>
16	0.37	0.22	0.72	0.991	0.05	6	<sup>g,h</sup>
17	0.61	0.46	0.71	0.960	0.10	6	<sup>g,h</sup>
18	-3.1 <sup>i</sup>	—	—	—	—	2	<sup>g</sup>
19	-1.5 <sup>i</sup>	—	—	—	—	2	<sup>g</sup>
20	0.94	0.79	0.75	0.993	0.04	7	<sup>d</sup>
	(0.66)	0.51	0.58	0.992	0.04	5	<sup>j</sup>
21	0.57	0.42	0.81	0.996	0.03	7	<sup>d</sup>
22	1.45	1.30	0.69	0.990	0.04	7	<sup>d</sup>
	(1.13)	0.98	0.54	0.997	0.02	5	<sup>j</sup>
23	0.65	0.50	0.73	0.991	0.04	7	<sup>d</sup>
24	0.72	0.57	0.79	0.997	0.02	8	<sup>k</sup>
25	1.47	1.32	0.75	0.996	0.03	7	<sup>k</sup>
26	-0.75	-0.90	0.77	0.979	0.07	8	<sup>k</sup>
27	-1.42	-1.57	0.84	0.988	0.06	7	<sup>k</sup>
28	1.26	1.11	0.78	0.997	0.025	7	<sup>d</sup>
29	-0.51	-0.66	0.82	0.995	0.04	7	<sup>d</sup>
30	0.14	-0.01	0.73	0.988	0.07	5	<sup>h</sup>

<sup>a</sup> Determined by <sup>1</sup>H-NMR in CDCl<sub>3</sub> at 20°C. Equilibrium constant  $K_T = [\mathbf{B} + \mathbf{B}']/[\mathbf{A-E} \text{ and } \mathbf{Z}]$ . In order to obtain the best comparable results, in the whole series  $K_T$  is calculated as  $[\mathbf{B} + \mathbf{B}']/[\mathbf{A-E}]$  for the norbornane derivatives **26** and **27**. <sup>b</sup> Standard error of slope. <sup>c</sup> For the series **13**, **20-23**, **25**, **27**, and **29**: X = 4-Me<sub>2</sub>N, 4-MeO, 4-Me, H, 4-Cl, 3-NO<sub>2</sub>, 4-NO<sub>2</sub>. For **24** and **26**, the same, but with X = 3-Cl. For **14-17**, the same, but without X = 3-NO<sub>2</sub>. For **18** and **19**, X = H and 4-NO<sub>2</sub>. For **30**, X = 4-MeO, 4-Me, H, 4-Br, 4-NO<sub>2</sub>. <sup>d</sup> Data from Fülöp *et al.* (87JOC3821). <sup>e</sup> Averaged data for the system containing various substituents Y. <sup>f</sup> Data from Fülöp *et al.* (93T2115). <sup>g</sup> Data from Fülöp *et al.* (87T1863). <sup>h</sup> Data from Fülöp *et al.* (93JOC1967). <sup>i</sup> Estimated value. <sup>j</sup> Data (at 50°C) from Fülöp *et al.* (90ACS364). <sup>k</sup> Data from Fülöp *et al.* (91T4031).

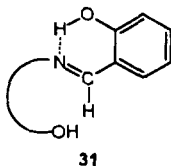
uted to an intramolecular hydrogen bond that stabilizes the open-chain tautomer (68JOC1), and to the decreased nucleophilicity of the phenolic OH group as compared with that of the CH<sub>2</sub>OH group in **28** (89MRC725). The introduction of a methyl group at position 2 slightly stabilizes the cyclic tautomer **30** versus **13** (*c* = 0.14), but this stability difference for the oxazine system is much smaller than that of 1,3-oxazolidines (**11** versus **3**, *c* = 1.29; see Table II). Introduction of a *tert*-butyl group on cyclopentane-fused derivatives **16-19** led to some stabilization of the ring form [94ACH(131)435]. The steric and electronic effects of the substituents have been discussed quite thoroughly in a recent review [94ACH(131)697].

The equilibrium between the two epimeric cyclic tautomers **B** and **B'** was studied (90ACS364; 91T2229) in the formation of perhydrobenzoxazines **20** and **22**. The time-dependent  $^1\text{H}$ -NMR spectra of the reaction mixtures of aminoalcohol and benzaldehyde in  $\text{CDCl}_3$  solution revealed the kinetically and thermodynamically favored epimers. The ratio  $[\text{B}]/[\text{B}']$  depends on the structure of the connecting link, the substituent X in the benzaldehyde ring, the temperature, and the reaction time. The condensation of *cis*-2-aminomethylcyclohexanol with *p*-nitrobenzaldehyde under mild conditions gives the imine product **21A**. This compound undergoes a solid-state rearrangement to **21B'**, which was followed by solid-state CP/MAS NMR. The rearrangement reaction shows an activation energy of  $20.3 \pm 3.0$  kcal/mol (95MRC600).

The *E/Z* equilibrium of the open-chain tautomers may exert an influence on the ring-chain equilibria just discussed, but this problem has not been studied. In order to obtain the best comparable results for the whole series of systems **13**–**30**, the ring-chain equilibrium constants for the norbornane derivatives **26** and **27** were calculated as  $K_T = [\text{B} + \text{B}']/[\text{A-E}]$ , i.e., those involving only the *E* isomer of the open-chain form (91T4031).

The slope coefficients  $\rho$  are nearly identical for all series,  $0.76 \pm 0.04$  at  $20^\circ\text{C}$  (see Table IV), but decrease with increasing temperature (90ACS364).

Strong stabilization was established for the open-chain tautomer of *o*-hydroxyphenyl derivatives **20**–**23** and **28** ( $\text{X} = 2\text{-OH}$ ) (88T2993). This is caused by the formation of an intramolecular hydrogen bond of type **31**. Substitution of the phenolic hydroxy for a methoxy group ( $\text{X} = 2\text{-MeO}$ ) shifts the equilibrium dramatically in favor of the cyclic tautomer.



For the system **13** ( $\text{X} = \text{H}, \text{MeO}, \text{Cl}$ ), the temperature dependence of the ring-chain equilibrium constant has been measured and the thermodynamic parameters have been calculated (91ZPK1052). For **13** ( $\text{X} = \text{H}$ ),  $-\Delta H^\circ = 2.1 \pm 0.1$  kcal/mol and  $-\Delta S^\circ = 7.9 \pm 0.1$  cal/mol K (in trichloroethylene).

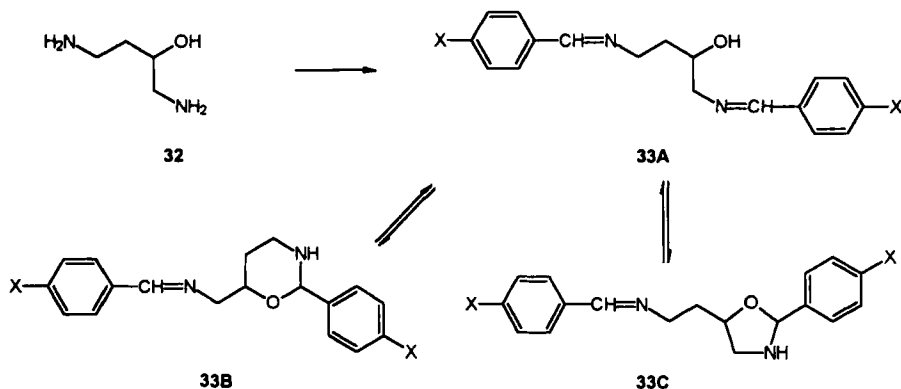
Use of the Palm-Koppel equation (72MI1; 77MI1; 88MI1) led to a good correlation ( $r = 0.986$ ) (91ZPK1052) between the constants of the ring-chain equilibrium **13A**  $\rightleftharpoons$  **13B** ( $\text{X} = \text{H}$ ) measured ( $^1\text{H}$ -NMR) in ten deuterated solvents and the sum of solvent polarity, polarizability, general acidity,

and general basicity contributions. All regression coefficients ( $y$ ,  $p$ ,  $e$ ,  $b$ ) were negative, showing that all solvation factors described by the Palm-Koppel equation influence the equilibrium in the same direction, destabilizing the cyclic tautomer with increasing solvent polarity. The equilibrium constant calculated in this way for **13** ( $X = H$ ) in the gas phase is  $K_T = 2.0$  ( $\log K_T = 0.30$ ). The corresponding  $\log K_T$  value determined by mass spectrometry [91OMS(36)438] in the gas phase for the same **13** ( $X = H$ ) varies from  $-0.708$  to  $+0.277$  [the intercept calculated by regression analysis,  $\log(K_T)_0$ , from  $-0.49$  to  $-0.03$ ], depending on the ionization energy (70 or 14 eV) and on the peaks used for the tautomer ratio calculations. The calculated  $\log K_T$  value (91ZPK1052) refers to ambient temperature, whereas the ion source temperature in these mass-spectrometric experiments was  $170^\circ\text{C}$ ; thus the agreement obtained may be considered good enough. Mass spectrometry demonstrated [91OMS(36)438] that the equilibrium **13A**  $\rightleftharpoons$  **13B** ( $X = \text{Me}_2\text{N}$ ,  $\text{MeO}$ ,  $\text{Me}$ ,  $\text{H}$ ,  $\text{Cl}$ ,  $\text{NO}_2$ ) really does exist in the gas phase and resembles that found in nonpolar solvents. The poor correlation coefficients  $r = 0.711\text{--}0.931$  obtained by using different peak intensity ratios and different ionizing electron energies (14 and 70 eV) reflect the difficulty of attributing fragment ions to a particular tautomer. The ionization energy has no influence on the electronic effects exerted by substituent  $X$ , as is obvious from the almost identical slope  $\rho$  values, while  $\log(K_T)_0$  depends strongly on the ionization energy and on the peaks chosen as quantitative characteristics of the open-chain or cyclic tautomer. Mass-spectrometric investigation of benzoxazines **28** does not give clear evidence for the presence of the ring-chain equilibrium in the gas phase, the fragmentation pathway of the cyclic tautomer being predominant. It has been concluded [91OMS(36)438] that the mass-spectrometric method used gives only qualitative or semiquantitative results, and that other methods are needed for the quantitative investigation of ring-chain equilibria in the gas phase [see also 83MI2; 91JCS(P2)735; 94H1093]. Measurements of the ring-chain equilibrium constant for the correspondingly substituted tetrahydro-1,3-oxazines and 1,3-oxazolidines were used to estimate  $\sigma^+$  for several substituents such as 2-, 3-, or 4-pyridyl (in  $\text{CDCl}_3$ ) (90MI2; 91ACS273) and 2- or 3-furyl, 2-pyrrolyl, and 3-thienyl in  $\text{CDCl}_3$  solution and in the gas phase (94H1093).

When trifunctional aminoalcohols such as hydroxyputrescine, 3-amino-1,2-propanediol, and 2-amino-1-phenyl-1,3-propanediol were used, three- to five-component equilibria were observed.

From hydroxyputrescine **32** with two equivalents of aromatic aldehyde, formation of the open form **33A** and tetrahydrooxazine **33B** occurred. Small amounts of the five-membered oxazolidine isomer **33C** were also present, but this was not determined accurately (83JOC5043).





The ratio of **33A** and **33B** proved to be slightly solvent-dependent (Table V). The reactions of 3-amino-1,2-propanediol with substituted aromatic aldehydes in  $\text{CDCl}_3$  resulted in five-component ring-chain tautomeric equilibria. Besides the open-chain form **34A**, two epimeric oxazolidines (**34B** and **34B'**) and two epimeric tetrahydro-1,3-oxazines (**34C** and **34C'**) were identified in the tautomeric mixture. The proportions of the tautomers in the equilibrium for  $\text{X} = p\text{-NO}_2$  were **[34A]** : **[34B]** : **[34B']** : **[34C]** : **[34C']** = 40.7 : 7.0 : 5.9 : 9.7 : 36.7 (94MI1, 94MI2).

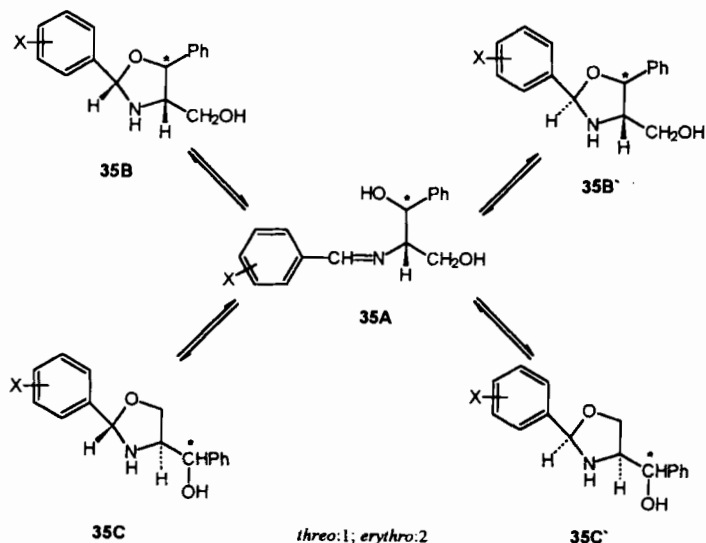
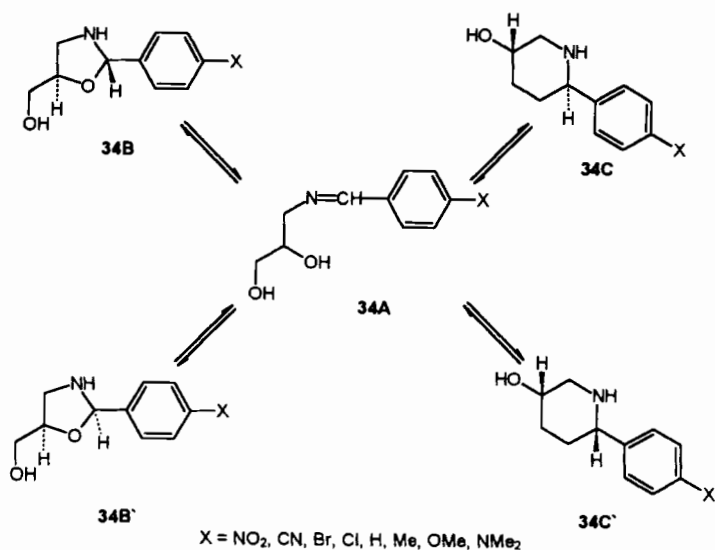
Another type of tautomer was formed in a five-component mixture in  $\text{CDCl}_3$  when (1*S*,2*S*)- or (1*R*\*,2*R*\*)-2-amino-1-phenyl-1,3-propanediol was reacted with substituted benzaldehydes; and tautomers **35A**, **35B**, **B'**, and **35C**, **C'** were identified in  $\text{CDCl}_3$  solution (94MI2).

An equilibrium between 5-hydroxymethyl-3,5-dimethyl-5,6-dihydro-2*H*-1,4-oxazin-2-one and its bicyclic tautomer **36A**  $\rightleftharpoons$  **36B** ( $\text{R} = \text{Me}$ ) was

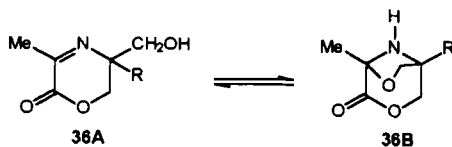
TABLE V  
SOLVENT DEPENDENCE OF THE RATIOS  
OF **33A** AND **33B**<sup>a</sup>

Solvent	X = H		X = NO <sub>2</sub>	
	<b>33A</b>	<b>33B</b>	<b>33A</b>	<b>33B</b>
C <sub>6</sub> D <sub>5</sub> N	4 : 1		2 : 1	
CD <sub>3</sub> CN			3 : 1	
C <sub>6</sub> D <sub>6</sub>			1 : 2	
CDCl <sub>3</sub>	3 : 1			

<sup>a</sup> Data from Tice and Ganem (83JOC5043). Determined by <sup>1</sup>H-NMR at room temperature.



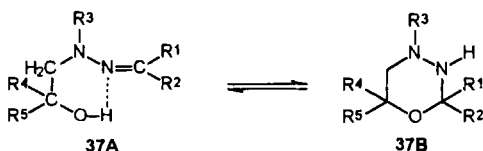
observed (87JOC3073) by means of  $^1\text{H}$ -NMR and UV spectroscopy. The equilibrium constant  $K_T$  varies from 0.22 to 1.0, depending on the solvent used, with a predominance of the open-chain tautomer in polar solvents. In  $\text{CF}_3\text{COOH}$ , the equilibrium is shifted toward the protonated open-chain tautomer ( $K_T < 0.04$ ). Recently, a similar equilibrium  $36\text{A} \rightleftharpoons 36\text{B}$  ( $\text{R} = \text{CH}_2\text{OH}$ ) was detected (93JOC7355).



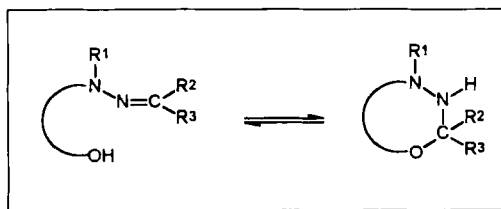
## 2. *N*-Hydroxyalkyl Hydrazones

The ring-chain tautomerism of the hydrazone derivatives has been discussed in a monograph (79MI1) and more thoroughly in a review (88KGS3).

Summarizing his own investigations, Potekhin calculated (89TH1) free enthalpy and entropy differences between tautomers **37A** and **37B** (Table VI). The introduction of an alkyl substituent on the nitrogen atom and the increase of its steric demand in the series  $R^3 = \text{Me} < \text{Et} < \text{Pr} < i\text{-Pr} < t\text{-Bu}$  shifted the equilibrium toward the cyclic tautomer.



It is presumed that the introduction of an alkyl group on the nitrogen weakens the intramolecular hydrogen bond  $\text{OH} \cdots \text{N}$  stabilizing the open-chain tautomer **37A**. This was corroborated by the predominance of the enthalpy change contribution in the free energy difference on passing from **37** ( $R^3 = \text{Me}$ ) to **37** ( $R^3 = t\text{-Bu}$ ). A certain role may also be played by the decrease in stability of the open-chain tautomer, due to the decreased rotational entropy of the molecule after introduction of the bulky substituent  $R^3$ ; but this is rather weakly reflected in the corresponding changes in the entropy contributions (Table VI).



SCHEME 1

TABLE VI  
EQUILIBRIUM **37A**  $\rightleftharpoons$  **37B** ( $R^1 = \text{Me}$ ) CONSTANTS AND THERMODYNAMIC PARAMETERS<sup>a</sup>

$R^2$	$R^3$	$R^4$	$R^5$	$K_T$ (at 35°C)	$-\Delta H^\circ$ kcal/mol	$-\Delta S^\circ$ kcal/mol
H	Me	H	H	0.90	5.7	18.7
H	Et	H	H	9.11	7.4	19.9
H	<i>t</i> -Bu	H	H	10.0 (50°C)	8.1	20.6
H	Me	Me	H	7.14	6.2	16.7
H	Me	Me	Me	5.56	5.7	15.8
Me	Me	H	H	0.41	8.9	30.4
Me	Et	H	H	1.33	9.6	30.1
Me	<i>t</i> -Bu	H	H	10.0	10.3	28.7
Me	Me	Me	H	3.13	9.3	28.2
Me	Me	Me	Me	0.05	—	—

<sup>a</sup> Data from Potekhin (89TH1).  $K_T$  determined by  $^1\text{H-NMR}$  in tetrachloroethylene.

The introduction of only one methyl group on the  $\alpha$ -carbon atom with respect to the hydroxy group (**37**,  $R^4 = \text{Me}$ ) stabilizes the cyclic tautomer. The presence of two methyl groups (**37**,  $R^4 = R^5 = \text{Me}$ ) exerts a less well expressed stabilizing effect when  $R^1 = R^3 = \text{Me}$  and  $R^2 = \text{H}$ , but an entirely opposite effect when  $R^1 = R^2 = R^3 = \text{Me}$ . This is presumed (89TH1) to be caused by nonbonded 2,6-diaxial (2-Me and 6-Me) interactions in the chair conformer of perhydro-1,3,4-oxadiazine **37B**.

For cyclohexane *trans*-fused hydrazone analogs of **37** ( $R^1 = \text{H}$ ,  $R^2 = \text{Ar}$ ,  $R^3 = \text{Me}$ ,  $\text{CH}_2\text{Ph}$ ), the presence of only the open-chain form was observed. The  $\text{C}=\text{N}$   $^{13}\text{C}$ -chemical shifts of hydrazones were analyzed for the first time in terms of separate resonance and inductive effects by using the dual-substituent-parameter approach (94JOC5895).

### 3. *N*-Hydroxyalkyl and *N*-Carboxyalkyl Nitrones

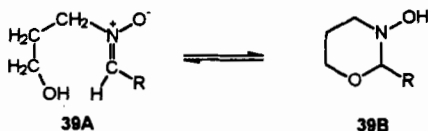
Several examples of ring-chain tautomerism are known where the cyclic tautomer is formed as a result of an intramolecular hydroxy group addition to the  $\text{C}=\text{N}$  bond of nitrones, yielding hydroxylamine derivatives.

Infrared and  $^1\text{H-NMR}$  spectroscopy provided no evidence of the presence of the cyclic tautomer **38B** in solutions of *C*-aryl- (77CB2067) and *C*-(2-furyl)-*N*-(2-hydroxyalkyl)aldonitrones (83CB27). However, chemical reactions, e.g., acylation, gave derivatives of both open-chain and cyclic tautomers. Mixtures of the isomers were detected in  $\text{CDCl}_3$  solutions of *C*-alkyl-*N*-(hydroxyalkyl)aldonitrones **38** ( $R^1 = \text{H}$ ;  $R^2 = \text{alkyl}$ ) and the corresponding acetone nitrones **38** ( $R^1 = R^2 = \text{Me}$ ) (77CB2090; 82LA1712).

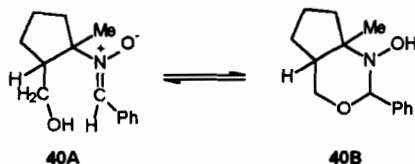
The isomer ratios determined (77CB2067; 82LA1712) could not be regarded as equilibrium constants because different isomer ratios were obtained for several distillation fractions or for freshly distilled and recrystallized products after dissolution in  $\text{CDCl}_3$ . Apparently, the equilibration  $\mathbf{38A} \rightleftharpoons \mathbf{38B}$  proceeds very slowly; hence the  $\text{CDCl}_3$  solutions had not been allowed to stand long enough for equilibrium to be reached before the  $^1\text{H-NMR}$  spectra were recorded.



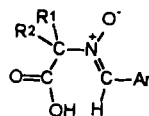
No cyclic tautomers of *C*-aryl- (83LA1937) and *C*-cyclohexyl-*N*-(3-hydroxypropyl)nitron **39** ( $\text{R} = \text{Ar}$ ,  $\text{C}_6\text{H}_{11}$ ) (84CZ283) were observed in solution on  $^1\text{H-NMR}$  spectroscopy. However, acylation of these nitrones gave *O*-acyl derivatives with the cyclic structure. A mixture of two isomers ( $[\mathbf{B}]/[\mathbf{A}] = 0.43$ ,  $^1\text{H-NMR}$ ) was detected (84CZ283) in a  $\text{CDCl}_3$  solution of the nitron **39** ( $\text{R} = \text{Me}$ ).



Rapid column chromatography permitted isolation of both isomers **40A** and **40B** (79JOC1819). When they were allowed to stand in  $\text{CDCl}_3$  solution for several hours, the equilibrium mixture ( $K_T \approx 1.0$ ) was obtained.

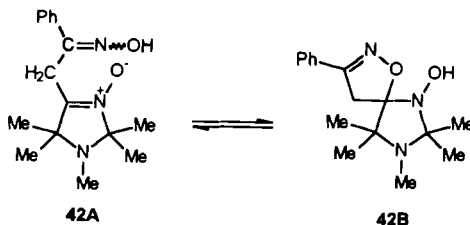
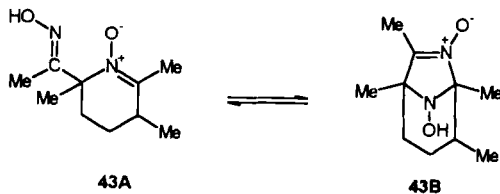


The  $^1\text{H-NMR}$  data indicated that *C*-aryl-*N*-(2-carboxyalkyl)nitrones exist only as the open-chain isomers **41A** in solution. However, in acylation reactions, they formed *O*-acyl derivatives with the cyclic structure, whereas alkylation with phenacyl bromide led to the open-chain esters (84LA1545).

**41A**

#### 4. *C-Hydroxyiminoalkyl Nitrones*

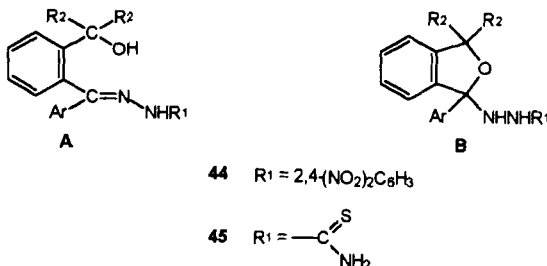
The ring-chain equilibrium **42A**  $\rightleftharpoons$  **42B** [ $K_T \approx 0.67$  in  $(\text{CD}_3)_2\text{SO}$ ,  $^1\text{H-NMR}$ ] has been observed (91KGS912). A similar tautomerism of a condensed imidazole derivative (**43A**  $\rightleftharpoons$  **43B**) had been reported previously [86JPR(328)589, 86JPR(328)597]. For a review on earlier investigations in this field, see (87MI2).

**42A****42B****43A****43B**

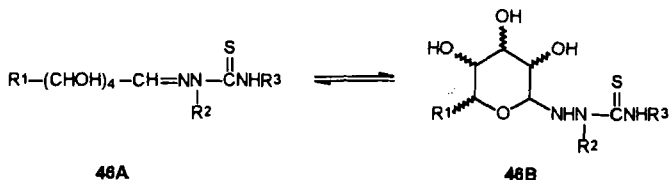
#### 5. *Hydrazones and Thiosemicarbazones of Hydroxy Aldehydes and Ketones*

Ultraviolet and  $^1\text{H-NMR}$  spectroscopic studies have shown (78ZOR2420) that most 2-(*o*-aroylphenyl)propan-2-ol 2,4-dinitrophenylhydrazones exist as stable cyclic phthalanes **44B** ( $\text{R}^2 = \text{Me}$ ;  $\text{Ar} = \text{XC}_6\text{H}_4$ ,  $\text{X} = \text{H}$ , 4-Me, 2-MeO, 3-MeO, 4-MeO). For the 3-tolyl derivative **44** ( $\text{R}^2 = \text{Me}$ ;  $\text{Ar} = 3\text{-MeC}_6\text{H}_4$ ), both isomers were isolated and a slow isomerization **44A**  $\rightarrow$  **44B** was observed in the solution. The cyclic isomer of 2-methoxy derivative **44B** ( $\text{R}^2 = \text{Me}$ ;  $\text{Ar} = 2\text{-MeOC}_6\text{H}_4$ ) is stabilized by an intramolecular hydro-

gen bond (MeO...H—N). Stable open-chain isomers have been obtained only for derivatives containing one or two *o*-methyl substituents in the aryl group (**44A**, R<sup>2</sup> = Me; Ar = 2-MeC<sub>6</sub>H<sub>4</sub> or 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>). Similarly, thiosemicarbazones of 2-(*o*-aroylphenyl)propan-2-ol **45** (R<sup>2</sup> = Me) or 3-(*o*-aroylphenyl)pentan-3-ol **45** (R<sup>2</sup> = Et) containing various substituents on the aryl group exist as stable cyclic phthalanes **45B** (86ZOR724). The stable open-chain isomer was obtained only for **45A** (R = Me; Ar = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>). A slow isomerization **45B** → **45A** was observed in ethanol solution only for phthalanes containing an *o*-tolyl group (**45B**, R = Me, Et; Ar = 2-MeC<sub>6</sub>H<sub>4</sub>).

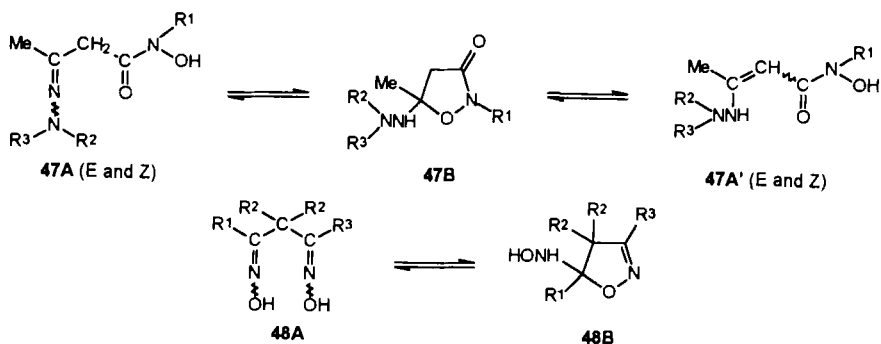


The ring-chain equilibrium **46A**  $\rightleftharpoons$  **46B** was revealed by  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectroscopy (93ZOR278) in solutions of D-glucose, D-mannose, D-galactose, and D-arabinose thiosemicarbazones. The equilibrium state depends rather unpredictably on the structures of the initial monosaccharide and of the substituents  $\text{R}^2$  and  $\text{R}^3$  in the thiosemicarbazone moiety. In solutions of D-fructose thiosemicarbazones, pyranose and furanose tautomers participate in the equilibrium.



### 6. Hydrazones of 3-Oxohydroxamic Acids

5-Hydrazinoisoxazolidin-3-ones, which exist in  $\text{CDCl}_3$  solution only as the cyclic tautomers **47B**, exhibit a five-component equilibrium (see Table VII) in  $(\text{CD}_3)_2\text{SO}$  or  $(\text{CD}_3)_2\text{NCDO}$  solutions (92KGS424). There are too few derivatives to establish the regularities of the influence of the structure on this complex equilibrium.



### 7. Dioximes of 1,3-Diketones and 3-Oxoaldehydes

Dioximes of 1,3-diketones or 3-oxoaldehydes exist in solution as open-chain tautomers **48A**, represented by three or four geometric isomers (*EE*, *EZ*, *ZE*, and *ZZ*; when  $R^1 = R^3$ , *EZ* and *ZE* are identical), or as an equilibrium shifted strongly in favor of the open-chain tautomers (88ZOR2287). The derivatives with  $R^1 = R^3$  have only the open-chain structure. The greater the difference in the steric demands of the substituents  $R^1$  and  $R^3$ , the more stable is the cyclic tautomer **48B**, which is formed by intramolecular NOH group addition to the sterically less hindered  $C=N$  group (see Table VIII). The sensitivity of the ring-chain equilibrium constant to the change in substituent X in the aryl group for the derivatives **48** ( $R^1 = \text{Me}$ ;  $R^2 = \text{XC}_6\text{H}_4$ ) is low, but well expressed for the character of the solvent used. The cyclic tautomer **48B** is more stable in  $\text{CDCl}_3$  solution. Increase of the solvent proton-accepting ability strongly stabilizes the open-chain tautomers owing to the presence of two more acidic  $=N-OH$  groups in comparison with one less acidic hydroxylamine OH group in the cyclic tautomer. For the benzoylacetone dioxime **48** ( $R^1 = \text{Me}$ ;  $R^2 = \text{H}$ ;  $R^3 = \text{Ph}$ ) in  $\text{CDCl}_3$ ,  $K_T = 3.54$ ; in  $\text{CD}_3\text{OD}$ ,  $K_T = 0.25$ ; in  $\text{C}_5\text{D}_5\text{N}$ ,  $K_T = 0.03$ ; and in  $(\text{CD}_3)_2\text{SO}$ ,  $K_T = 0.02$  ( $^1\text{H-NMR}$ ).

TABLE VII  
CONTENTS OF THE EQUILIBRIUM MIXTURES AND EQUILIBRIUM CONSTANTS OF  
5-HYDRAZINOXAZOLIDIN-3-ONES (**47**)<sup>a</sup>

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Contents (%)				B	$K_T = [\text{B}]/[\Sigma\text{A}]$
			A - E	A - Z	A' - E	A' - Z		
Ph	Me	Me	10	6	22	18	44	0.79
Ph	PhCH <sub>2</sub>	PhCH <sub>2</sub>	8	9	60	7	16	0.19
PhCH <sub>2</sub>	H	PhCH <sub>2</sub> CO	55	40	—	—	5	0.05

<sup>a</sup> Data from Zelenin *et al.* (92KGS424). Determined by  $^1\text{H-NMR}$  in  $(\text{CD}_3)_2\text{SO}$ .



TABLE VIII  
RING-CHAIN EQUILIBRIUM CONSTANTS OF  
1,3-DICARBONYL COMPOUND DIOXIMES  
(**48A**  $\rightleftharpoons$  **48B**,  $R^2 = H$ )<sup>a</sup>

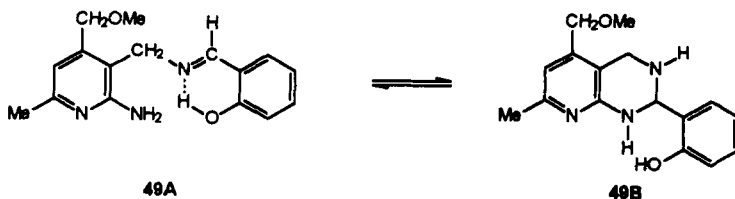
$R^1$	$R^3$	$K_T = [B]/[\Sigma A]$
H	<i>i</i> -Bu	0.23
H	Ph	0.75
H	4-BrC <sub>6</sub> H <sub>4</sub>	0.85
Me	<i>i</i> -Pr	1.10 <sup>b</sup>
Me	Ph	0.23
Me	4-MeOC <sub>6</sub> H <sub>4</sub>	0.19
Me	4-ClC <sub>6</sub> H <sub>4</sub>	0.25

<sup>a</sup> Data from Ershov *et al.* (88ZOR2287). Determined by <sup>1</sup>H-NMR in (CD<sub>3</sub>)<sub>2</sub>CO at 30°C, 6 days or more after dissolution. <sup>b</sup> In CDCl<sub>3</sub>.

## B. ADDITION OF AN NH GROUP

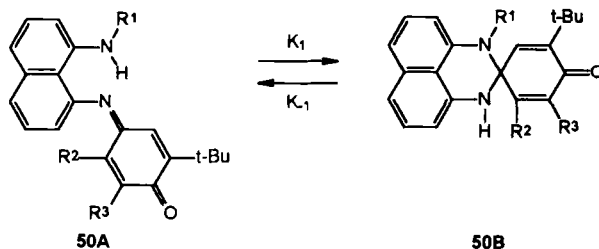
### 1. Imines Containing an NH Group in the Substituent on the Nitrogen Atom

The slowly reached (24 hours in CDCl<sub>3</sub> solution at 20°C,  $K_T = 1$ ) equilibrium **49A**  $\rightleftharpoons$  **49B** has been demonstrated by UV, IR, and <sup>1</sup>H-NMR spectroscopy (85MI2). The open-chain tautomer is stabilized by an intramolecular hydrogen bond.



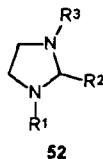
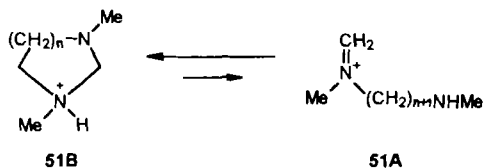
The formation of a cyclic tautomer was observed [88DOK(301)902] for the system **50A**  $\rightleftharpoons$  **50B** ( $R^1 = H, Me, i\text{-Bu}$ ;  $R^2 = H$ ;  $R^3 = t\text{-Bu}$ ) as a consequence of intramolecular N—H group addition to the quinonimine C=N bond. By means of UV spectroscopy, thermodynamic and kinetic parameters were determined for the tautomeric interconversions of quinonimine **50** ( $R^1 = R^2 = H$ ;  $R^3 = t\text{-Bu}$ ) in octane solution:  $K_T = 20$ ,  $\Delta G^\circ = 1.7$  kcal/mol,  $k_1 = 1 \times 10^{-4}$  s<sup>-1</sup>,  $k_{-1} = 5 \times 10^{-6}$  s<sup>-1</sup>,  $\Delta G_1^\ddagger = 22.5$  kcal/mol,  $\Delta G_{-1}^\ddagger = 24.2$  kcal/mol. The high activation barrier ( $\Delta G^\ddagger$ ) allows these

interconversions to be ascribed to molecular rearrangements (isomerization), but not to tautomerism (see I-8). The transformation **50B**  $\rightarrow$  **50A** is photostimulated, i.e., facilitated for the excited state, while the reverse rearrangement is thermostimulated. An electrochemical activation of these transformations has been reported (92AGE1498). The addition of nucleophilic reagents (amines, etc.) slows down the dark transformation **50A**  $\rightleftharpoons$  **50B**, which is caused by the increased activation barrier (92ZOR1093). A similar rearrangement has been reported (90ZOR1106) for naphthoquinonimine system **50** ( $R^1 = H$ ;  $R^2, R^3 = -CH=CHCH=CH-$ ). For another similar system, see (93ZOR1915).

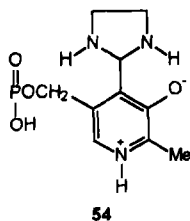


<sup>1</sup>H-NMR spectroscopy revealed the equilibrium **51A**  $\rightleftharpoons$  **51B** ( $n = 1, 2$ ) (80JA3588) in solutions of 1,3-dimethylimidazolidine and 1,3-dimethylperhydropyrimidine in CF<sub>3</sub>COOH. Increase of the temperature shifts the equilibrium in favor of the protonated open-chain tautomer. The tautomerization rate is higher for the five-membered ring system ( $n = 1$ ), thus contradicting the Baldwin rules [76JCS(CC)234; 92MI1; 93ACR476]. The coalescence temperature of the equilibration **51A**  $\rightleftharpoons$  **51B** ( $n = 1$ ) was found to be 90°C, which corresponds to an activation barrier of 16.7 kcal/mol. The investigation (87JOC68) of a series of 1,3-diazolidines **52** in CF<sub>3</sub>COOH showed that the structure of the *N*-alkyl substituent has a slight influence on the ring-chain equilibrium ( $K_T \sim 19$ ) and the rate of equilibrium ( $\Delta G^\ddagger = 16.3\text{--}17.3$  kcal/mol). Unsymmetrically substituted derivatives **52** ( $R^1 \neq R^3$ ) form two different open-chain tautomers, as expected. The introduction of an aryl group on the nitrogen atom results in decomposition in CF<sub>3</sub>COOH solution. An aryl group at position 2 ( $R^2 = \text{Ph}$ ), especially if it contains an electron-donating substituent (**52**,  $R^2 = 4\text{-MeOC}_6\text{H}_4$ ,  $4\text{-MeCONHC}_6\text{H}_4$ ), stabilizes the open-chain tautomer, due to the resonance delocalization, as shown in formula **53**. However, for 2-aryl-substituted derivatives, a side reaction was observed, probably involving water addition to the iminium double bond, which makes investigation of the ring-chain equilibrium difficult. For derivatives **52** ( $R^1 = R^3 = \text{Me}$ ;  $R^2 = \text{Ar}$ ), the content of the

protonated open-chain tautomer in  $\text{CF}_3\text{COOH}$  at  $30^\circ\text{C}$  is 28% when  $\text{R}^2 = \text{Ph}$ , 40% when  $\text{R}^2 = 4\text{-MeOC}_6\text{H}_4$ , and 33% when  $\text{R}^2 = 4\text{-MeCONHC}_6\text{H}_4$  ( $^1\text{H-NMR}$ ).

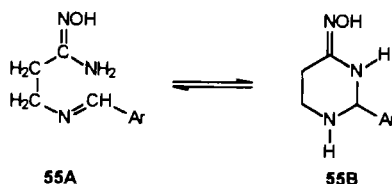


The thermodynamic and kinetic characteristics of an intramolecular transimination reaction observed in solutions containing pyridoxal-5-phosphate and ethylenediamine have been investigated (75JA6530). The open-chain structure Schiff bases and the cyclic tautomers such as **54** are in equilibrium in aqueous solution over the pH range 7.5–14, but these equilibria are rather complex owing to the different states of the ionization (protonation) in both tautomers. The ring-chain equilibrium constant (the sum of all cyclic tautomers versus all open-chain tautomers) varies by less than a factor of 4 over the pH range 7–14. At pH 14,  $K_T = 1.2$ ; at pH 10,



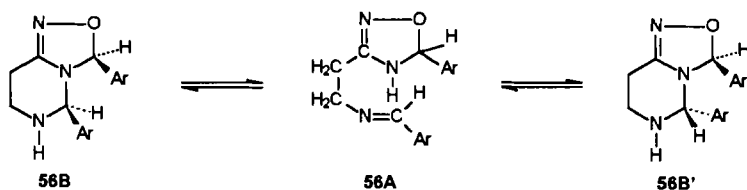
$K_T = 0.84$ ; and at pH 7,  $K_T = 0.36$ . The rate of ring-chain interconversions obtained from temperature-jump kinetic experiments appears to be hydronium-ion-catalyzed in the pH range 11.5–13, with rate constants reaching about  $10^5 \text{ s}^{-1}$ . It was presumed that the cyclic tautomers **54** can serve as kinetically competent intermediates for transimination sequences at the active sites of pyridoxal-P-dependent enzymes.

As shown by  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectroscopy (91CB1199), 3-arylidene-aminopropionamide oximes in  $(\text{CD}_3)_2\text{SO}$  solution slowly (in *ca.* 48 hours) reached the equilibrium **55A**  $\rightleftharpoons$  **55B**. The presence of an electron-withdrawing substituent in the aryl group shifts the equilibrium in favor of the cyclic tautomer: In  $(\text{CD}_3)_2\text{SO}$  at  $20^\circ\text{C}$ , when  $\text{Ar} = \text{Ph}$ ,  $K_T = 0.09$ ; for  $2\text{-ClC}_6\text{H}_4$ ,  $K_T = 0.18$ ; for  $4\text{-ClC}_6\text{H}_4$ ,  $K_T = 0.12$ ; and for  $3\text{-NO}_2\text{C}_6\text{H}_4$ ,  $K_T = 0.33$ . Decreasing solvent proton-accepting ability stabilizes the cyclic tautomer: In  $\text{CDCl}_3$ , for  $\text{Ar} = \text{Ph}$ ,  $K_T = 0.47$ . The derivatives **55A** containing electron-donating substituents in the aryl group ( $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$ ,  $4\text{-Me}_2\text{NC}_6\text{H}_4$ ,  $\text{PhCH}=\text{CH}$ ) exist as open-chain isomers only. For the derivatives **55** ( $\text{Ar} = \text{XC}_6\text{H}_4$ ;  $\text{X} = \text{H}$ ,  $2\text{-Cl}$ ,  $4\text{-Cl}$ ,  $3\text{-NO}_2$ ), both tautomers have been isolated in the solid state. Their interconversions were carried out by dissolution in methanol or ethanol and precipitation after cooling, by the addition of either diethyl ether (**A**  $\rightarrow$  **B**) or hexane (**B**  $\rightarrow$  **A**).



The  $^1\text{H}$ -,  $^{13}\text{C}$ - and  $^{15}\text{N}$ -NMR, and IR spectroscopic data indicate a similar three-component equilibrium **56B**  $\rightleftharpoons$  **56A**  $\rightleftharpoons$  **56B'**, involving two diastereomeric cyclic tautomers (91CB2065). In  $\text{CDCl}_3$  solution, starting from solid **56B** ( $\text{Ar} = \text{Ph}$ ), the equilibrium state was reached after 6 days. The solid-state structure of the tautomer **56B** ( $\text{Ar} = \text{Ph}$ , *cis* configuration of the phenyl groups) was confirmed by X-ray diffraction analysis. Again, for this system, increasing electron-withdrawing ability of the substituents in the aryl group stabilizes the cyclic tautomer: In  $\text{CDCl}_3$  at  $20^\circ\text{C}$  for  $\text{Ar} = \text{Ph}$ ,  $K_T = [\text{B} + \text{B}']/[\text{A}] = 3.17$ ,  $K_D = [\text{B}]/[\text{B}'] = 2.04$ ; for  $2\text{-ClC}_6\text{H}_4$ ,  $K_T = 2.57$ ,  $K_D = 3.80$ ; and for  $4\text{-ClC}_6\text{H}_4$ ,  $K_T = 3.55$ ,  $K_D = 2.39$ . Because of the insolubility of the derivatives **56** ( $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$ ,  $\text{PhCH}=\text{CH}$ ) in  $\text{CDCl}_3$ , the equilibrium constant measurements were carried out in  $(\text{CD}_3)_2\text{SO}$ : for  $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$ ,  $K_T = 0.43$ ,  $K_D = 4.0$ ; and for  $\text{PhCH}=\text{CH}$ ,  $K_T = 0.09$ ,  $K_D = 7.0$ . As stated earlier, such a solvent change destabilizes the cyclic

tautomer; for the last two derivatives, the strong equilibrium shift in favor of the open-chain tautomer is caused by the substituent electronic effect and by the solvent change effect. All the compounds but one (**56A**, Ar = PhCH=CH) have been isolated in the solid state as cyclic isomers **56B**, with the *cis* configuration of the aryl groups [91CB2065; 92JCS(P1)3069; 94H2051].

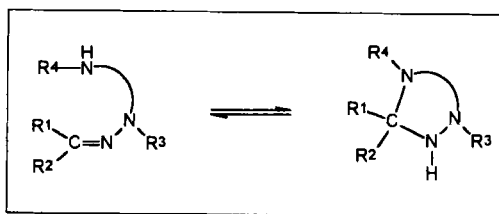


It is apparent that the increasing conformational rigidity of the connecting link on passing from **55** to **56** strongly stabilizes the cyclic tautomer:  $(K_T)^{56/}$   $(K_T)^{55} = 6.74$  in  $\text{CDCl}_3$  for Ar = Ph.

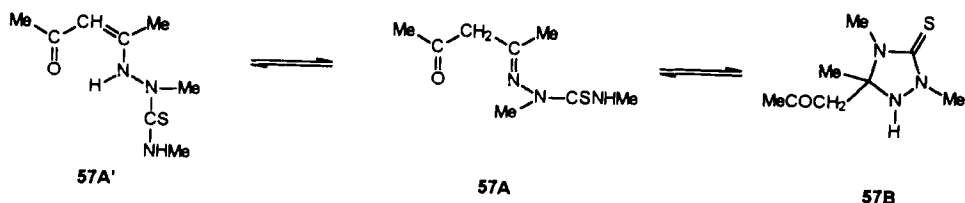
## 2. Hydrazones Containing an NH Group in the Substituent on the Nitrogen Atom

Ring-chain tautomerism established by intramolecular reversible N—H group addition to the hydrazone C=N bond has been studied in a wide series of derivatives with different structures containing hydrazone N—H groups [for a review, see (88KGS3)]. The cyclic tautomers mostly involve five- or six-membered rings.

a. *Five-Membered Rings.* Pentane-2,4-dione 2,4-dimethylthiosemicarbazone exists as enhydrazine **57A'** in  $(\text{CD}_3)_2\text{SO}$  or  $(\text{CD}_3)_2\text{NCDO}$  solution just after dissolution. After several hours, *ca.* 15% of thiosemicarbazone **57A** together with the cyclic tautomer **57B** was detected; but after 7 days, the solutions contained 85–90% of 1,2,4-triazolidine-3-thione **57B** (90KGS1260).



SCHEME 2



The equilibrium  $\text{58A} \rightleftharpoons \text{58B}$  in  $(\text{CD}_3)_2\text{SO}$  solutions of acetone *S*-alkyl-isothiosemicarbazonium halides **58** ( $\text{R}^4 = \text{R}^5 = \text{Me}$ ;  $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ) was established (91KGS1515) by means of  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR measurements. It is clear from Table IX that the introduction of an alkyl substituent into the thiosemicarbazonium moiety, especially when  $\text{R}^3 = \text{Me}$ , shifts the equilibrium in favor of the cyclic tautomer **58B**. Increasing steric demands of the substituent  $\text{R}^1$  slightly destabilize the cyclic tautomer. The corresponding benzaldehyde derivatives **58**, even though both contain *N*-methyl groups in the thiosemicarbazonium moiety ( $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$ ;  $\text{R}^4 = \text{H}$ ;  $\text{R}^5 = 4\text{-MeOC}_6\text{H}_4$ ), exist as stable open-chain isomers in the solid state and in solution, presumably because the open-chain structure is stabilized by conjugation of the aryl group with the  $\text{C}=\text{N}$  bond in **58A**. Mass-spectrometric investigations (91KGS1515) revealed the influence of a similar structural factor in the gas phase.

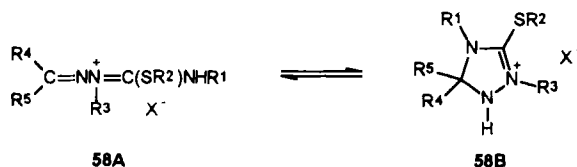
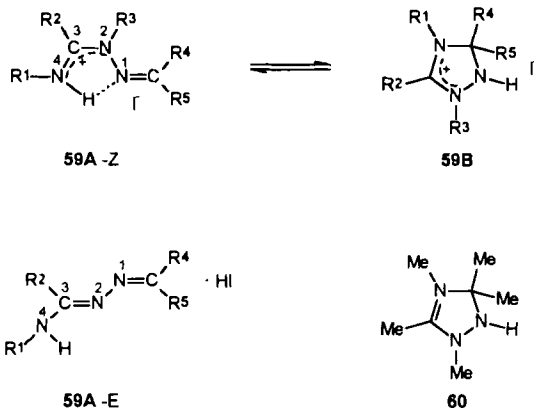


TABLE IX  
RING-CHAIN EQUILIBRIUM  $\text{58A} \rightleftharpoons \text{58B}$   
( $\text{R}^2 = \text{R}^4 = \text{R}^5 = \text{Me}$ ) CONSTANTS<sup>a</sup>

$\text{R}^1$	$\text{R}^3$	$K_T$
H	H	0.03
Me	H	0.37
Et	H	0.18
$\text{PhCH}_2$	H	0.20
Me	H	9.0
Me	Me	>30 (100% <b>B</b> )

<sup>a</sup> Data from Zelenin *et al.* (91KGS1515). Determined by  $^1\text{H}$ -NMR in  $(\text{CD}_3)_2\text{SO}$ .

Zelenin and co-workers (80KGS1138; 81ZOR1825) first discovered the ring-chain equilibrium  $59\mathbf{A} \rightleftharpoons 59\mathbf{B}$  in solutions of 1-(2-propylidene)benzamidrazone hydroiodide  $59$  ( $R^1 = R^3 = \text{H}$ ;  $R^2 = \text{Ph}$ ;  $R^4 = R^5 = \text{Me}$ ), which exists in the solid state as an open-chain isomer  $59\mathbf{A-Z}$ , stabilized by an intramolecular hydrogen bond. The iodide of 1-(2-propylidene)-3-methylacetamidrazonium  $59$  ( $R^1 = R^2 = R^4 = R^5 = \text{Me}$ ;  $R^3 = \text{H}$ ) exists in the solid state as the stable open-chain isomer and does not exhibit ring-chain equilibrium in solution. Replacement of the hydrogen atom on N(2) with a methyl group ( $R^3 = \text{Me}$ ) stabilizes the cyclic form. Thus, the iodide  $59$  ( $R^1 = \text{H}$ ;  $R^2 = R^3 = R^4 = R^5 = \text{Me}$ ) exists as a cyclic isomer in the solid state and exhibits a ring-chain equilibrium in solution. The equilibrium constant depends on the solvent: In  $(\text{CD}_3)_2\text{NCDO}$ ,  $K_T = 2.13$ ; in  $(\text{CD}_3)_2\text{SO}$ ,  $K_T = 2.23$ ; and in  $\text{CDCl}_3$ ,  $K_T = 7.33$ . The free bases have the cyclic structure  $60$  and do not exhibit ring-chain equilibrium.



The influence of the structural factors on the equilibrium  $59\mathbf{A} \rightleftharpoons 59\mathbf{B}$  has been studied (82KGS1264; 94KGS1415; 86TH1, 86ZOR500) in a large series of acet- and benzamidrazonium iodides of type  $59$ . For  $R^3 = \text{H}$ , the acetamidrazonium derivatives  $59$  ( $R^2 = \text{Me}$ ) exist as open-chain isomers  $59\mathbf{A-E}$  in the solid state, and the presence of the cyclic tautomer could not be detected in solution. It was presumed (82KGS1264) that the increased stability of the open-chain isomer is due to the unfavorable position of the NH and C=N(1) groups in the molecule of  $59\mathbf{A-E}$  with respect to the ring closure. When  $R^3 = \text{H}$ , the benzamidrazonium derivatives  $59$  ( $R^2 = \text{Ph}$ ) in the solid state possess the open-chain structure  $59\mathbf{A-Z}$ . In  $(\text{CD}_3)_2\text{SO}$  or  $(\text{CD}_3)_2\text{NCDO}$  solution, the equilibrium mixtures were detected 24 hours after dissolution, but the amount of the cyclic tautomer  $59\mathbf{B}$  ( $R^1 = \text{H}$  or  $\text{Me}$ ;  $R^4 = \text{Me}$ ;  $R^5 = \text{Me}$ , *t*-Bu, Ph) did not exceed *ca.* 10% at equilibrium.

The free energies of the two tautomers become closer upon the introduction of an alkyl substituent on N(2), which increases steric demands ( $R^3 = \text{Me, Pr}$ ). The series of *N*(2)-methyl-substituted derivatives (Table X) shows that the transition from the acetamidrazonium **59** ( $R^2 = \text{Me}$ ) to the benzamidrazonium iodides **59** ( $R^2 = \text{Ph}$ ) leads to stabilization of the cyclic tautomer, as already observed (82KGS1264) for the series of *N*(2)-unsubstituted derivatives. Surprisingly, an increase in the number ( $R^4 = R^5 = \text{Me}$ ;  $R^4 = \text{H}$ ;  $R^5 = \text{Me}$ ) and steric demands of the substituents  $R^4$  and  $R^5$  in the alkylidene fragment shifts the equilibrium in favor of the cyclic tautomer **59B** (84KGS1415). This was explained by the greater sensitivity of the open-chain tautomer to the increase in the overall steric strain in the molecule. A methyl substituent at N(4) ( $R^1 = \text{Me}$ ) also stabilizes the cyclic tautomer. An aryl group as substituent  $R^5$ , when  $R^4 = \text{H}$ , stabilizes the open-chain tautomer owing to the free-energy gain caused by the conjugation  $\text{Ar}-\text{C}=\text{N}$  in **59A**. The introduction of a methyl group in the arylidene fragment ( $R^4 = \text{Me}$ ;  $R^5 = \text{Ar}$ ) diminishes the conjugation due to steric hindrance and, as a consequence, slightly decreases the stabilization of the open-chain tautomer (see Table X). The introduction of an electron-donating

TABLE X  
SOLID-STATE STRUCTURE AND RING-CHAIN  
EQUILIBRIUM CONSTANTS OF ACET- AND  
BENZAMIDRAZONIUM IODIDES (**59A**  $\rightleftharpoons$  **59B**,  
 $R^1 = \text{H}$ ,  $R^3 = \text{Me}$ )<sup>a</sup>

$R^2$	$R^4$	$R^5$	Structure in solid state	$K_T$
Me	H	Me	<b>A</b>	0.69
Me	Me	Me	<b>B</b>	2.23
Me	Me	<i>t</i> -Bu	<b>B</b>	8.09
Me	H	Ph	<b>A</b>	<0.03
Me	Me	Ph	<b>A</b>	0.25
Me	Me	4-NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>A</b>	<0.03
Me	Me	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>A</b>	0.06
Me	Me	4-ClC <sub>6</sub> H <sub>4</sub>	<b>A</b>	0.28
Me	Me	3-ClC <sub>6</sub> H <sub>4</sub>	<b>A</b>	0.43
Me	Me	Me	<b>B</b>	6.69 <sup>b</sup>
Me	Me	Me	<b>B</b>	>30 <sup>c</sup>
Ph	H	Me	<b>B</b>	2.33
Ph	Me	Me	<b>B</b>	4.56
Ph	Me	<i>t</i> -Bu	<b>B</b>	24
Ph	Me	Me	<b>B</b>	11.5 <sup>b</sup>
Ph	H	Ph	<b>A</b>	<0.03

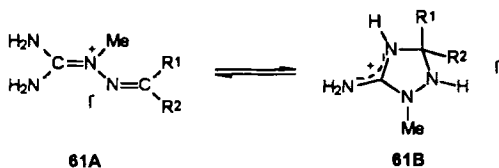
<sup>a</sup> Data from Pinson *et al.* (84KGS1415; 86TH1).  
Determined by <sup>1</sup>H-NMR in (CD<sub>3</sub>)<sub>2</sub>SO at 20°C, 72  
hours after dissolution. <sup>b</sup>  $R^3 = \text{Pr}$ . <sup>c</sup>  $R^1 = \text{Me}$ .



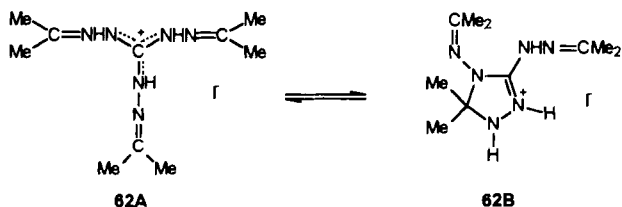
substituent X onto the aryl group (**59**,  $R^4 = \text{Me}$ ;  $R^5 = \text{XC}_6\text{H}_4$ ) decreases the  $\text{C}=\text{N}(1)$  carbon atom electrophilicity and therefore stabilizes the open-chain tautomer. This stabilization may also be caused by the strengthening of the intramolecular hydrogen bond in the open-chain tautomer **59A-Z**. For several derivatives of this series, the thermodynamic parameters have been determined (86TH1), and it has been concluded that the stability of the tautomers **59A-Z** and **59B** depends to a large extent on solvation effects. For the iodide **59A** ( $R^1 = R^4 = \text{H}$ ;  $R^2 = R^3 = R^5 = \text{Me}$ ), which exists in the solid state as the open-chain isomer, a shift of the equilibrium toward the cyclic tautomer was observed in the series of solvents  $\text{CDCl}_3 < \text{CD}_3\text{COD} < (\text{CD}_3)_2\text{NCDO} < (\text{CD}_3)_2\text{SO} < \text{DCOND}_2$ . But for the cyclic isomer iodide **59B** ( $R^1 = \text{H}$ ;  $R^2 = \text{Ph}$ ;  $R^3 = R^4 = R^5 = \text{Me}$ ), the influence of the solvent on the equilibrium state was in the reverse direction. It was therefore concluded (86TH1) that the strong solvation effects level the influence of the structural factor on the state of the equilibrium **59A**  $\rightleftharpoons$  **59B**.

Depending on the substitution pattern in the amidrazonium and 1,3-diketone moieties, 1,3-diketone monobenz- or monoacetamidrazonium salts (86ZOR500) may exist exclusively as the open-chain isomer **59A-Z** ( $R^1 = R^3 = \text{H}$ ;  $R^2 = \text{Ph}$ ;  $R^4 = \text{Me}$ ;  $R^5 = \text{CMe}_2\text{COMe}$ ) or exclusively as the cyclic isomers **59B** ( $R^1 = \text{H}$ ;  $R^2 = \text{Ph}$ ;  $R^3 = R^4 = \text{Me}$ ;  $R^5 = \text{CH}_2\text{COMe}$ ); or they may exist as a tautomeric mixture containing not only **59A-Z**, but also the enhydrazine-like open-chain tautomer and the cyclic pyrazoline tautomer formed by intramolecular  $\text{N}(2)-\text{H}$  group ( $R^3 = \text{H}$ ) addition to the second  $\text{C}=\text{O}$  group of the 1,3-diketone.

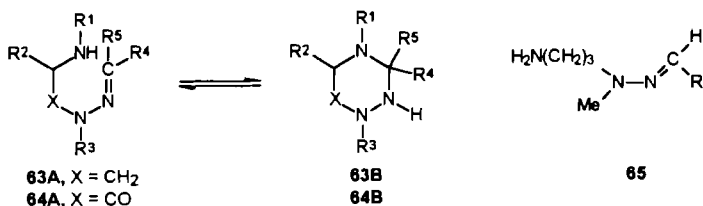
A similar influence of the substituents on the equilibrium **61A**  $\rightleftharpoons$  **61B** was detected (87KGS1071) in a series of 1-alkylidene(or arylidene)-2-methylaminoguanidinium iodides. In the solid state, all investigated derivatives possess the open-chain structure **61A**. The arylidene derivatives exist only as open-chain isomers **61A** ( $R^1 = \text{H}$ ;  $R^2 = 4\text{-XC}_6\text{H}_4$ ,  $\text{X} = \text{H}, \text{MeO}, \text{NH}_2$ ) in  $(\text{CD}_3)_2\text{SO}$  and  $(\text{CD}_3)_2\text{NCDO}$  solution. In the solutions of the alkylidene derivatives, ring-chain equilibrium appears: In  $(\text{CD}_3)_2\text{NCDO}$  for **61** ( $R^1 = \text{H}$ ;  $R^2 = \text{Me}$ ),  $K_T = 0.08$ ; in  $(\text{CD}_3)_2\text{SO}$  for **61** ( $R^1 = R^2 = \text{Me}$ ),  $K_T = 1.70$ ; and for **61** ( $R^1 = \text{Me}$ ;  $R^2 = \text{Et}$ ),  $K_T = 0.88(1)$ . These data are clearly in contradiction with the influence of the substituents in the alkylidene group on the equilibrium **59A**  $\rightleftharpoons$  **59B** (see Table X), where the transition from derivative **59** ( $R^4 = R^5 = \text{Me}$ ) to **59** ( $R^4 = \text{Me}$ ;  $R^5 = t\text{-Bu}$ ) increases the equilibrium constant.



A slowly reached (in 24 hours) equilibrium  $62\mathbf{A} \rightleftharpoons 62\mathbf{B}$  was observed (93KGS135) in a  $(\text{CD}_3)_2\text{SO}$  solution of this (isopropylideneamino)guanidinium iodide ( $K_T = 0.25$ ).



b. *Six-Membered Rings.* Potekhin and Lobanov have investigated the ring-chain equilibrium in solutions of the aldehyde and ketone *N*-(2-aminoethyl)hydrazones  $63\mathbf{A} \rightleftharpoons 63\mathbf{B}$  (83ZOR2310; 91KGS1392) and *N*-(2-aminoacyl)hydrazones  $63\mathbf{A} \rightleftharpoons 64\mathbf{B}$  (80ZOR2297; 83TH1). Replacement of the methylene group ( $\text{X} = \text{CH}_2$ ) in the connecting link with a carbonyl group ( $\text{X} = \text{CO}$ ) leads to an equilibrium shift in favor of the cyclic tautomer  $64\mathbf{B}$ . The  $\text{C}=\text{O}$  group participation in competition with the nitrogen atom electron lone pair decreases the  $p-\pi$  conjugation between this lone pair and the hydrazone  $\text{C}=\text{N}$  bond in  $64\mathbf{A}$ , thereby destabilizing the open-chain tautomer  $64\mathbf{A}$ .



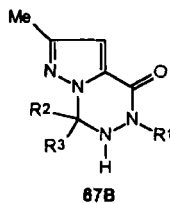
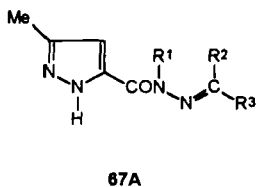
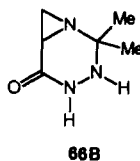
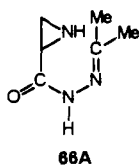
As observed by Potekhin and co-workers in a series of *N*-(2-hydroxyethyl)hydrazones (I-175), the most significant factor in the stabilization of the cyclic tautomer is the presence of the alkyl substituent on the hydrazone nitrogen atom ( $63, 64, \text{R}^3 = \text{alkyl}$ ). Thus, when  $\text{R}^3 = \text{H}$ , *N*-(2-alkylaminoacyl)hydrazones in the solid state and in solution exist only as the open-chain isomers  $64\mathbf{A}$  (78ZOR1086). The introduction of an alkyl substituent ( $\text{R}^3 = \text{Me}$ ) and the increase of its steric demands ( $\text{R}^3 = \text{Pr}$ ) strongly shift the equilibrium  $64\mathbf{A} \rightleftharpoons 64\mathbf{B}$ , in favor of the cyclic tautomer. A similar equilibrium shift was observed for the system  $63\mathbf{A} \rightleftharpoons 63\mathbf{B}$ .

Increases in the steric demands of the substituent on the amine nitrogen atom in the series  $\text{R}^1 = \text{Me} < \text{Et} < i\text{-Pr} < t\text{-Bu}$  shift the equilibria  $63\mathbf{A}$

$\rightleftharpoons$  **63B** and **64A**  $\rightleftharpoons$  **64B** toward the open-chain tautomers; but on change from  $R^1 = H$  to  $R^1 = Me$ , a slight shift of the equilibrium **63A**  $\rightleftharpoons$  **63B** in favor of the cyclic tautomer was detected. A similar pattern of the influence of the N-substituent was observed in the series of ketoamides (I-49). The introduction of a methyl group on the  $\alpha$ -carbon atom in the aminoacyl moiety ( $R^2 = Me$ ) slightly destabilizes the cyclic tautomer.

An increase in the number of methyl substituents on the alkylidene carbon atom of the hydrazones **63** ( $R^4 = R^5 = H < R^4 = H; R^5 = Me < R^4 = R^5 = Me$ ) displaces the equilibrium in favor of the open-chain tautomer. The steric demands of the open-chain **63A** and the cyclic **63B** tautomers clearly differ from those in the systems **59** and **61**, where an opposite effect was detected. An increase in the temperature of the solutions shifts the equilibrium toward the open-chain tautomer. In most cases, an equilibrium shift in the same direction was observed on increase of the solvent polarity (83ZOR2310). *N*-(3-Aminopropyl)-*N*-methylhydrazones **65** ( $R = H, Me$ ) exist as stable open-chain isomers and do not exhibit any tendency to seven-membered-ring closure (83ZOR2310).

For *N*-acylhydrazones containing an N—H group in the heterocycle moiety, **66A** and **B** (85KGS774), **67A** and **B** (84MI1), the open-chain and cyclic isomers have been isolated. The gas-chromatographic behavior of the latter isomeric hydrazones was studied and the ability of this method to allow the distinction and determination of the isomers was shown (84MI1).



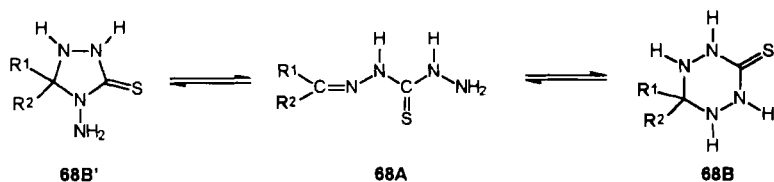
The tautomerism **68A**  $\rightleftharpoons$  **68B** resulting from intramolecular addition of a thiohydrazone N—H group to the hydrazone C=N bond has been observed (69JOC756; 84OMR6) in solutions of monothiocarbonohydrazones of ke-

TABLE XI  
RING-CHAIN EQUILIBRIUM CONSTANTS OF  
THIOCARBONOMOONHYDRAZONES  
(**68A**  $\rightleftharpoons$  **68B**,  $R^2 = H$ )<sup>a</sup>

$R^1$	$R^2$	$K_T = [B]/[A]$
H	<i>t</i> -Bu	0.43
H	cyclo-C <sub>6</sub> H <sub>11</sub>	>24
Me	Me	5.25
Me	Et	4.0
Me	<i>i</i> -Pr	0.34
Me	Ph	0.54 <sup>b</sup>

<sup>a</sup> Data from Rayendran and Jain (84OMR6).  
Determined by <sup>1</sup>H-NMR in (CD<sub>3</sub>)<sub>2</sub>SO at 36°C 24  
hours after dissolution. <sup>b</sup> Data from Zelenin *et al.*  
(90TL3927).

tones and of some aldehydes containing branched substituents (Table XI). The condensation products of thiocarbonohydrazide with formaldehyde, unbranched aliphatic aldehydes, phenylacetaldehyde, and cyclohexanone exist in solution only as the cyclic isomers **68B**. The derivatives of substituted aromatic aldehydes **68** ( $R^1 = H$ ;  $R^2 = 3\text{-HOC}_6\text{H}_4$ ,  $4\text{-HO-3-MeC}_6\text{H}_3$ , 2-furyl,  $4\text{-XC}_6\text{H}_4$ ; X = OH, MeO, Me<sub>2</sub>N, H, Cl, NO<sub>2</sub>), cinnamaldehyde and benzylideneacetone, exist in (CD<sub>3</sub>)<sub>2</sub>SO solution as stable open-chain isomers **68A**, due to the conjugation  $\text{Ar}-\text{C}=\text{N}-\text{N}$ , or as the enlarged conjugated system in the case of the last two derivatives. The pinacolone derivative, containing a highly hindered  $\text{C}=\text{N}$  bond, conforms to the nearly pure open-chain isomer **68A** ( $R^1 = \text{Me}$ ;  $R^2 = t\text{-Bu}$ ). It is shown in Table XI that increase of the steric demands of the substituent  $R^2$  (when  $R^1 = \text{Me}$ ) displaces the equilibrium in favor of the open-chain tautomer.

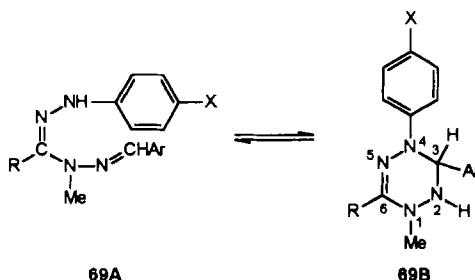


A more thorough investigation (90TL3927), carried out by means of <sup>1</sup>H-, <sup>13</sup>C-, and <sup>15</sup>N-NMR spectroscopy, showed that in (CD<sub>3</sub>)<sub>2</sub>SO solution the acetone and phenylacetone derivatives **68** actually exhibit a three-component equilibrium **68B'**  $\rightleftharpoons$  **68A**  $\rightleftharpoons$  **68B**, caused by competitive formation of a five- or six-membered ring due to intramolecular addition of either

an NH or NH<sub>2</sub> group to the C=N bond. For **68** (R<sup>1</sup> = R<sup>2</sup> = Me) in (CD<sub>3</sub>)<sub>2</sub>SO solution, 5% of **A**, 70% of **B**, and 25% of **B'** were determined; and for **68** (R<sup>1</sup> = Me; R<sup>2</sup> = PhCH<sub>2</sub>), 17% of **A**, 70% of **B**, and 13% of **B'**. On the basis of <sup>1</sup>H- and <sup>13</sup>C-NMR investigations of a large group of variously substituted aldehyde and ketone thiocarbonohydrazones, the general conclusion has been reached (93ZOR588) that the three-component equilibrium **68B'** ⇌ **68A** ⇌ **68B** can be observed in solutions of ketone thiocarbonohydrazones **68** (R<sup>1</sup> = Me; R<sup>2</sup> = Me, Et, Bu, *i*-Bu, PhCH<sub>2</sub>; or R<sup>1</sup>, R<sup>2</sup> = -(CH<sub>2</sub>)<sub>5</sub>-) only if they do not contain a sterically demanding substituent (e.g., *t*-Bu) on the keto group. The introduction of a substituent (Me, *i*-Pr, Ph) on N(5) hinders the formation of six-membered cyclic tautomer **68B**. In (CD<sub>3</sub>)<sub>2</sub>SO solution, *N*(5)-substituted ketone thiocarbonohydrazones exhibit the equilibrium **68A** ⇌ **68B'**. The introduction of a methyl group on N(2) favors the formation of five-membered cyclic tautomer **68B'**. For the mass-spectrometric data on the ring-chain equilibrium of the bithiocarbonohydrazones of ketones in the gas phase, see (94KG1525).

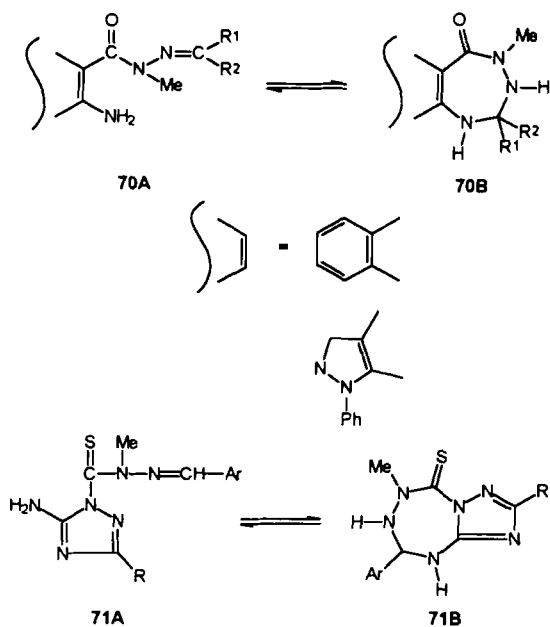
An equilibrium of the pyranose versus the corresponding perhydro-*s*-tetrazine-3-thione (as in **68B**) was demonstrated (93ZOR278) in solutions of D-glucose and D-galactose monothiocarbonohydrazones.

In a large series of 6-substituted 3,4-diaryl(or 3-heteroaryl-4-aryl)-1-methyl-1,2,3,4-tetrahydro-*s*-tetrazines, the equilibrium **69A** ⇌ **69B** was observed and the equilibrium constants were measured (<sup>1</sup>H-NMR) in CDCl<sub>3</sub> solution (89H1163; 91H1063). The stability of the cyclic tautomer **69B** was increased on increase of the electron-donating ability of the substituent X (X = NO<sub>2</sub>, COOMe, COMe, CN, F, Cl, Br, I, H, Me, MeO) and on decrease of the electron-withdrawing ability of the substituent R in the series R = COMe < COOMe < Ph. Both these factors increase the nucleophilicity of the adding NH group in the open-chain tautomer **69A**. The aryl substituents increase the stability of the cyclic tautomer in the following sequence: Ar = 2-thienyl < 2-furyl < 2-pyridyl < phenyl. 6-Alkyl-substituted derivatives exist only as the cyclic tetrazines **69B** (R = alkyl).



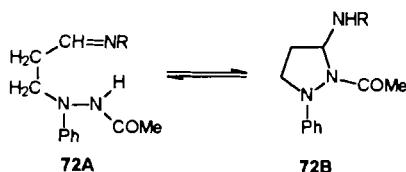
X = H, Me, MeO, F, Cl, Br, I, CN, COMe, NO<sub>2</sub>, COOMe

c. *Seven-Membered Rings*. The only known case of seven-membered-ring formation caused by an intermolecular reversible NH group addition to a hydrazone C=N bond is the system **70A**  $\rightleftharpoons$  **70B** [86ACH(123)55]. The *N*-(*o*-aminobenzoyl)- and *N*-(5-amino-1-phenyl-4-pyrazolylcarbonyl)-*N*-methylhydrazones of acetaldehyde, acetone, and cyclohexanone exist as stable seven-membered rings **70B**, and those of benzaldehyde as the open-chain isomers **70A**. In the CDCl<sub>3</sub> solution of acetophenone *N*-(*o*-aminobenzoyl)-*N*-methylhydrazone, a slowly reached (in 8 hours at 20°C) equilibrium was detected ( $K_T$ )  $\sim$  1.0, <sup>1</sup>H-NMR). *N*-Unsubstituted hydrazones (NH in place of NMe) are not capable of ring formation (92T531). A more thorough investigation (90MI1) using long-range <sup>1</sup>H-<sup>13</sup>C chemical shift correlation 2D experiments confirmed the existence, in a CDCl<sub>3</sub> solution of *o*-aminobenzoyl derivative **70** ( $R^1 = H$ ;  $R^2 = t\text{-Bu}$ ), of a three-component equilibrium involving *E* and *Z* geometric isomers of the open-chain tautomer **70A**. A four-component equilibrium was observed in solution for *o*-aminobenzoyl derivative **70** ( $R^1 = H$ ;  $R^2 = Ph$ ); this equilibrium involves two conformers of the seven-membered cyclic tautomer **70B** and the *E* and *Z* isomers of the open-chain tautomer **70A**. A similar tautomerism was found in the case of triazolo-fused tetrazepines **71** ( $R = \text{morpholino or methylthio}$ ). In CDCl<sub>3</sub> or (CD<sub>3</sub>)<sub>2</sub>SO, the ring-chain tautomeric equilibrium **71A**  $\rightleftharpoons$  **71B** was observed, and in some cases open and ring forms were isolated in the solid form (93JHC1009).

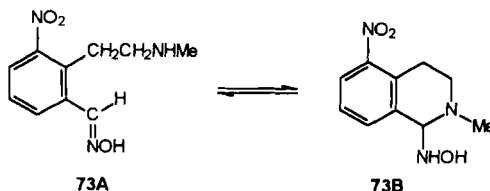


### 3. Imines and Oximes Containing an NH Group in the Substituent on the Carbon Atom

Mass-spectrometric investigation (86KGS1334) of 2-acetyl-3-amino-1-phenylpyrazolidines **72B** showed that in the gas phase equilibrium **72B**  $\rightleftharpoons$  **72A** exists. The ratio  $[\mathbf{72B}]/[\mathbf{72A}]$  in the gas phase is insensitive to changes in the electronic characteristics of substituent X ( $R = 4\text{-XC}_6\text{H}_4$ ; X = H, Me, MeO, Br, NO<sub>2</sub>), which seems rather astonishing. Replacement of the aryl group ( $R = 4\text{-XC}_6\text{H}_4$ ) by a benzyl group leads to an increase in intensity of the cyclic isomer fragment ion.



By means of solid-state <sup>1</sup>H-NMR spectroscopy, the open-chain structure of 2-(2-*N*-methylaminoethyl)-3-nitrobenzaloxime (**73A**) was corroborated (84CB702). In (CD<sub>3</sub>)<sub>2</sub>SO solution, the equilibrium **73A**  $\rightleftharpoons$  **73B** was detected ( $K_T = 0.54$ , <sup>1</sup>H-NMR).



### 4. Hydrazones Containing an NH Group in the Substituent on the Carbon Atom

On the basis of <sup>13</sup>C-NMR data, the equilibrium **74A**  $\rightleftharpoons$  **74B** in (CD<sub>3</sub>)<sub>2</sub>SO solution is established [86AP(319)910]. On change from **74** ( $R = \text{Ph}$ ) to **74** ( $R = \text{PhNHCO}$ ), the equilibrium is shifted in favor of the cyclic tautomer.

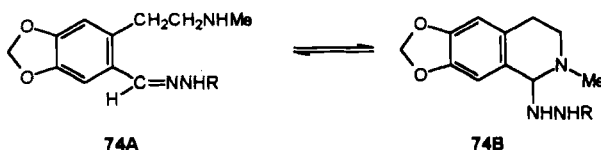
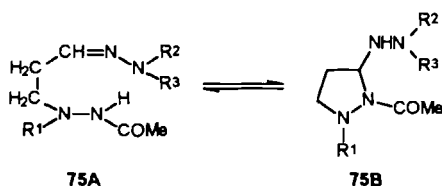


TABLE XII  
SOLID-STATE STRUCTURE AND RING-CHAIN EQUILIBRIUM CONSTANTS OF HYDRAZONES OF  
3-(*N'*-ACETYLHYDRAZINO)PROPANALS **75A**  $\rightleftharpoons$  **75B**<sup>a</sup>

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Structure in solid state	<i>K</i> <sub>T</sub>	
				in solution	in gas phase
<i>i</i> -Pr	Me	Me	<b>A</b>	—	0.2
Ph	Me	Me	<b>A</b>	—	—
Ph	H	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>A</b>	—	0.6
Ph	H	MeCO	<b>A</b>	—	0.8
<i>i</i> -Pr	H	PhCO	<b>B</b>	9 (CDCl <sub>3</sub> )	0.7
Ph	H	PhCO	<b>A</b>	0.18 [(CD <sub>3</sub> ) <sub>2</sub> NCDO]	1.5
<i>i</i> -Pr	H	PhCS	<b>B</b>	>30 [(CD <sub>3</sub> ) <sub>2</sub> NCDO]	—

<sup>a</sup> Data from Zelenin *et al.* determined by <sup>1</sup>H-NMR in solution (85KGS1238) and by mass spectrometry in the gas phase (86KGS1334).

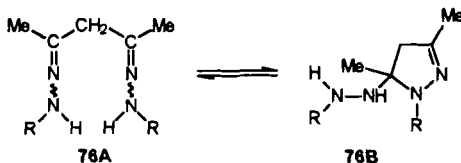
In contrast with the 3-(*N*-acetyl-*N*-*R*<sup>1</sup>-hydrazino)propanals, which exist as stable 3-hydroxypyrazolidines (84KGS659), the hydrazones of these aldehydes possess predominantly the open-chain structure **75A** (85KGS1238) (see Table XII). The equilibrium **75A**  $\rightleftharpoons$  **75B** was reached over several days. Increase of the solvent polarity stabilizes the open-chain tautomer **75A**. It is surprising that the thiobenzoyl derivative **75** (*R*<sup>1</sup> = *i*-Pr; *R*<sup>2</sup> = H; *R*<sup>3</sup> = PhCS), which is capable of 1,3,4-thiadiazoline ring closure (see **83B** in Section II,C,2), exists entirely in the pyrazolidine form **75B**, as distinct from other alkylidene derivatives of thiobenzhydrazide [82JC-S(CC)188; 82KGS904]. The main factor in the stabilization of the cyclic tautomer is apparently the presence of a branched alkyl substituent on the hydrazine nitrogen atom (*R*<sup>1</sup> = *i*-Pr). According to the mass-spectrometric data, the more expressed predominance of the open-chain form **75A** in the gas phase is obvious in comparison with the pyrazolidines **72B** (86KGS1334), formed by intramolecular addition of the same hydrazide NH group, but to the imine C=N bond.





Zelenin and co-workers have shown (85KGS854, 85KGS1000; 86KGS128; 87KGS1210; 88ZOR426) that the reaction products of 1,3-diketones with hydrazides in a molar ratio of 1:2 most frequently possess the cyclic structure of the corresponding 5-hydrazino-2-pyrazolines (such as **76B**). They can also be produced in the reactions between the corresponding hydrazine derivatives and 1-acyl-5-hydroxy-2-pyrazolines or 1-acyl-5-methylene-2-pyrazolines.

However, the equilibrium  $76A \rightleftharpoons 76B$  has been observed for some derivatives (87ZOB584), where the cyclic tautomer is formed by the intramolecular addition of one hydrazone NH group to the C=N bond of the other hydrazone moiety. Zelenin and co-workers (85KGS1000) applied the term "ring-ring tautomerism" to the more interesting phenomenon of an equilibrium between two isomeric 5-hydrazino-2-pyrazolines; such an equilibrium may be due either to an asymmetric structure of the initial 1,3-diketone containing different substituents on the two C=O groups (88KGS1358) or to the presence of different substituents in the two hydrazone moieties.



In general [for a review, see (92KGS851)], this type of equilibrium actually proceeds via the scheme ring-chain-ring, but with a very small concentration of the intermediate open-chain tautomer at equilibrium, which prevents its detection by the methods used for the investigation of these equilibria. The two cyclic tautomers may be formed either by the competitive intramolecular addition of two different nucleophilic groups XH to one multiple bond, or by the same process, but of one nucleophilic group to the two different polar multiple bonds.

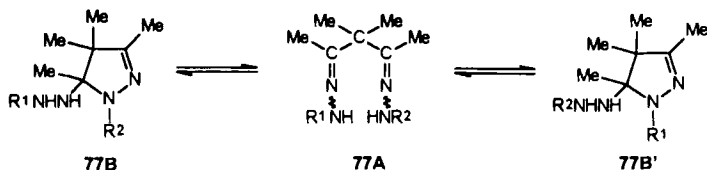
Pentane-2,4-dione reacts with 4-phenylsemicarbazide to form both isomers **76A** and **76B** ( $R = \text{PhNCO}$ ) (87ZOB584), and  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR methods have demonstrated that in solution an irreversible isomerization  $76A \rightarrow 76B$  proceeds at ambient temperature.

The bis-adduct of pentane-2,4-dione with aminoguanidinium nitrate, **76** [ $R = \text{H}_2\text{N}(\text{H}_2\text{N}^+=)\text{C}, \text{NO}_3$ ], exists in solution as an equilibrium mixture  $76A \rightleftharpoons 76B$ . In  $(\text{CD}_3)_2\text{NCDO}$ ,  $K_T = 0.43$ ; and in  $\text{D}_2\text{O}$ ,  $K_T = 13.3$  at  $90^\circ\text{C}$ .

The bis-adducts of pentane-2,4-dione with benzamidrazonium iodide, **76** [ $R = \text{Ph}(\text{H}_2\text{N}^+=)\text{C}, \text{I}^-$ ], possessing the open-chain structure in the solid state, exhibits the equilibrium  $76A \rightleftharpoons 76B$  in solution: in  $\text{CDCl}_3-(\text{CD}_3)_2\text{SO}$

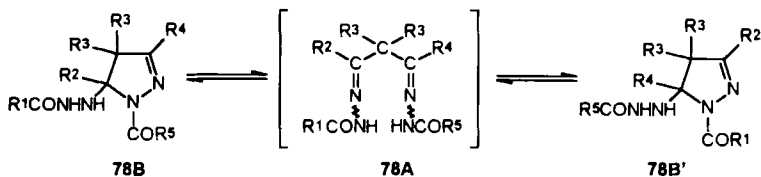
(2:1, v/v),  $K_T = 0.18$ . Replacement of the iodide by picrate leads to the derivative that exists in solution solely as the cyclic tautomer **76B**.

The bis-adducts of 3,3-dimethylpentane-2,4-dione with phenyl and 2,4-dinitrophenyl hydrazines **77** [ $R^1 = R^2 = \text{Ph}$ , 2,4-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>] have been obtained (85KGS854; 86ZOR1096; 88ZOR426), and the irreversible isomerization **77A**  $\rightarrow$  **77B** ( $R^1 = R^2 = \text{Ph}$ ) has been observed in benzonitrile solution at 60°C. The analogous isomerization for the 2,4-dinitrophenyl derivative does not take place at all. The isomerization **77A**  $\rightarrow$  **77B** ( $R^1 = R^2 = \text{Ph}$ ) has also been detected in the gas phase under the conditions of the mass-spectrometric experiment.



For  $R^1 \neq R^2$ , the equilibrium **77B**  $\rightleftharpoons$  **77B'** ( $R^1 = \text{Me}$ ,  $\text{PhCH}_2$ ;  $R^2 = \text{Ph}$ ) in the gas phase was confirmed (88ZOR426) by means of mass spectrometry. No mass-spectrometric evidence was obtained for the presence of the open-chain isomer **77A**.

The equilibrium between the two isomeric 1-acyl-5-acylhydrazino-2-pyrazolines **78B**  $\rightleftharpoons$  **78B'** was first detected (85KGS1000) by means of <sup>1</sup>H- and <sup>13</sup>C-NMR spectroscopy in solutions of the derivatives **78** ( $R^1 = R^5 = \text{Ph}$ ;  $R^2 = \text{Et}$ ;  $R^3 = \text{H}$ ;  $R^4 = \text{Me}$ ), with  $[\text{B}']/[\text{B}] = 0.66$ , and **78** ( $R^1 = 4\text{-ClC}_6\text{H}_4$ ;  $R^2 = R^3 = R^4 = \text{Me}$ ;  $R^5 = \text{Ph}$ ), with  $[\text{B}']/[\text{B}] = \text{ca. } 1$ , both in (CD<sub>3</sub>)<sub>2</sub>CO. Equilibrium was reached slowly at ambient temperature. The rate of the equilibration may be increased by elevation of the temperature or by the addition of catalytic amounts of trifluoroacetic acid to the solution.



With the aim of detection of the open-chain tautomer **78A**, the pentane-2,4-dione derivatives **78** ( $R^1 = R^5 = i\text{-Pr}$ ,  $i\text{-Bu}$ ,  $t\text{-Bu}$ ;  $R^2 = R^4 = \text{Me}$ ;  $R^3 = \text{H}$ ) containing sterically bulky substituents in the acyl group were

synthesized. However, it appears that all these derivatives exist solely as cyclic isomers **78B**  $\rightleftharpoons$  **78B'** in different solvents [(CD<sub>3</sub>)<sub>2</sub>NCDO, (CD<sub>3</sub>)<sub>2</sub>SO, (CD<sub>3</sub>)<sub>2</sub>CO, C<sub>5</sub>D<sub>5</sub>N, CD<sub>3</sub>CN, CDCl<sub>3</sub>] at temperatures from -40 to 140°C (88KGS1358).

Investigations of the influence of the structure of the substituent R<sup>4</sup> on the state of the equilibrium **78B**  $\rightleftharpoons$  **78B'** (R<sup>1</sup> = R<sup>5</sup> = Ph; R<sup>2</sup> = Me; R<sup>3</sup> = H) showed that increase of the steric demands of R<sup>4</sup> leads to a strong equilibrium shift toward **78B**. Apparently, of the two competitive intramolecular NH group addition pathways, the addition to the sterically less shielded C=N bond predominates (see Table XIII). The equilibrium **78B**  $\rightleftharpoons$  **78B'** was reached over several hours. The character of the solvent and temperature change exerted little influence on the equilibrium.

The reaction products of hydroxylamine with 1-alkyl-3,4,4-trimethyl-5-methylene-2-pyrazolines yield equilibrium mixtures of 5-hydroxylamino-2-pyrazolines versus 5-hydrazino-2-isoxazolines **79B**  $\rightleftharpoons$  **79B'** [86DOK(289)1132]. Such derivatives of unsubstituted pentane-2,4-dione exist in the solid state, in solution, or in the gas phase (89KGS927) only as isoxazolines (85KGS854). The equilibrium **79B**  $\rightleftharpoons$  **79B'** is caused by two competitive intramolecular reactions involving the open-chain tautomer **79A**: addition of a hydrazone NH group to the oxime C=N bond yields **79B**, but addition of the oxime OH group to the hydrazone C=N bond leads to the tautomer **79B'**. However, no <sup>1</sup>H- or <sup>13</sup>C-NMR evidence has been obtained for the presence of the open-chain tautomer **79A** in solution. By means of mass spectrometry, the presence of a small amount (*ca.* 5%) of **79A** (R = *i*-Pr or PhCH<sub>2</sub>) was detected (89KGS927) in the gas phase.

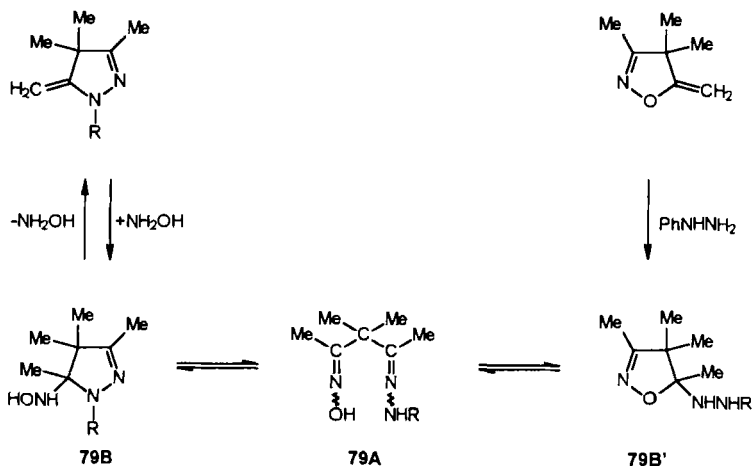


TABLE XIII  
EQUILIBRIUM  $78\mathbf{B} \rightleftharpoons 78\mathbf{B}'$  ( $R^1 = R^5 = \text{Ph}$ ;  
 $R^2 = \text{Me}$ ;  $R^3 = \text{H}$ ) CONSTANTS<sup>a</sup>

$R^4$	Solvent	$[\mathbf{B}']/[\mathbf{B}]$
H	$\text{C}_5\text{D}_5\text{N}$	30
Et	$(\text{CD}_3)_2\text{CO}$	0.67
Pr	$\text{CDCl}_3$	0.18
<i>i</i> -Pr	$(\text{CD}_3)_2\text{SO}$	0

<sup>a</sup> Data from Malov *et al.* (88KGS1358). Determined by  $^1\text{H}$ -NMR.

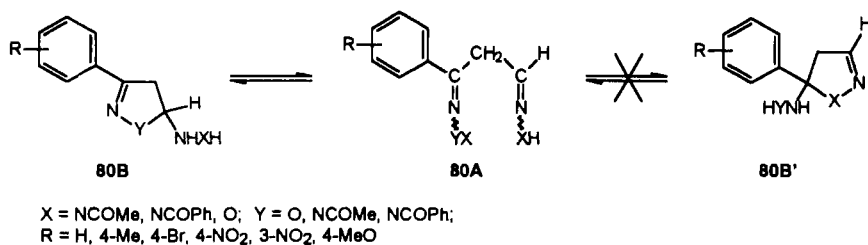
The equilibrium  $79\mathbf{B} \rightleftharpoons 79\mathbf{B}'$  was attained over several days at ambient temperature. Increase of the steric demands of the *N*-alkyl substituent R shifts the equilibrium toward the isoxazoline tautomer  $79\mathbf{B}'$  (see Table XIV). Increase of the solvent polarity stabilizes the pyrazoline tautomer  $79\mathbf{B}$ . In a large series of solvents such as  $\text{CCl}_4$ ,  $\text{C}_6\text{H}_6$ ,  $\text{CDCl}_3$ ,  $(\text{CD}_3)_2\text{CO}$ ,  $\text{C}_5\text{D}_5\text{N}$ ,  $\text{CD}_3\text{OD}$ ,  $\text{D}_2\text{O}$ , and  $(\text{CD}_3)_2\text{SO}$ , no correlation with the parameter  $E_T$  of the solvent used has been observed. Increase of the temperature of the solution in  $\text{CDCl}_3$  or  $(\text{CD}_3)_2\text{SO}$  leads to an equilibrium shift in favor of the isoxazoline tautomer  $79\mathbf{B}'$  because the pyrazoline tautomer  $79\mathbf{B}$  eliminates hydroxylamine, transforming into the initial 1-alkyl-3,

TABLE XIV  
SOLID-STATE STRUCTURE AND EQUILIBRIUM  $79\mathbf{B} \rightleftharpoons 79\mathbf{B}'$  CONSTANTS<sup>a,b</sup>

R	Structure in solid state	Solvent	$[\mathbf{B}']/[\mathbf{B}]$
Me	<b>B</b>	$\text{C}_6\text{H}_6$	1.0
		$(\text{CD}_3)_2\text{SO}$	0.05
Et	<b>B</b>	$\text{CDCl}_3$	5.67
		$(\text{CD}_3)_2\text{SO}$	0.33
		$\text{C}_5\text{D}_5\text{N}$ (at $-40^\circ\text{C}$ )	0.82
$\text{PhCH}_2$	<b>B</b>	$\text{CDCl}_3$	13.3
		$(\text{CD}_3)_2\text{SO}$	0.43
<i>i</i> -Pr	<b>B</b>	$\text{CDCl}_3$	>30
			(100% <b>B'</b> )
		$(\text{CD}_3)_2\text{SO}$	19
Ph	<b>B'</b>	$\text{CCl}_4$	>30
			(100% <b>B'</b> )
		$(\text{CD}_3)_2\text{SO}$	1.0

<sup>a</sup> The structure in the solid state is shown for the freshly synthesized derivatives. <sup>b</sup> Data from Zelenin *et al.* [86DOK(289)1132]. Determined by  $^1\text{H}$ -NMR.

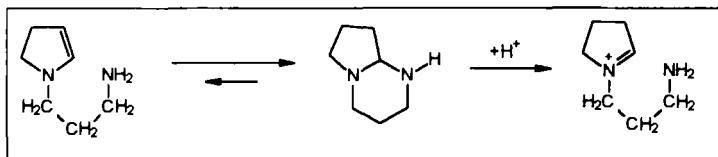
4,4-trimethyl-5-methylene-2-pyrazoline. For the *N*-ethyl derivative **79B** ( $R = \text{Et}$ ), such an elimination proceeds even at ambient temperature; therefore **79B** could not be isolated in the solid state. Pyrazolines **79B** ( $R = \text{PhCH}_2, i\text{-Pr}$ ) isomerize into the isoxazolines **79B'** on dissolution in  $\text{CDCl}_3$ ; and after removal of the solvent, these isoxazolines can be isolated as pure solid compounds. Pyrazoline **79B** ( $R = i\text{-Pr}$ ) undergoes such an irreversible isomerization even without the solvent: in 30 min after the synthesis, the solid derivative **79B** transforms into an oil that has the structure **79B'** according to its  $^1\text{H}$ -NMR data. The pyrazoline tautomer **79B** strongly predominates in the gas phase for the derivatives **79** ( $R = \text{Me}, \text{Et}$ ), but increase of the steric demands of the substituent  $R$  stabilizes the isoxazoline **79B'**. Thus, mass spectrometry revealed isomer proportions of 5% of **79A**, 13% of **B**, and 82% of **B'** (89KGS927) in the gas phase for the *N*-isopropyl derivative **79**.



An exceptionally high influence of the C-substituent at the  $\text{C}=\text{N}$  bond on the cyclization direction has been observed (89KGS927) in a large series of derivatives **80**. In the solid state and in solution in several solvents, these compounds exist solely as the isomer **80B**. Independently of the mutual disposition of the oxime and hydrazone moieties—i.e., for either  $X = \text{NCOR}$ ,  $Y = \text{O}$  or for  $X = \text{O}$ ,  $Y = \text{NCOR}$  and for  $X = Y = \text{NCOPh}$ —the intramolecular cyclization proceeds only along the path involving nucleophilic  $\text{XH}$  or  $\text{YH}$  group addition to the more reactive and less hindered aldoxime or aldohydrazone  $\text{C}=\text{N}$  bond. However, in the gas phase, the presence of small amounts of the isomers **80A** and **80B'** was detected.

## 5. Fused Systems

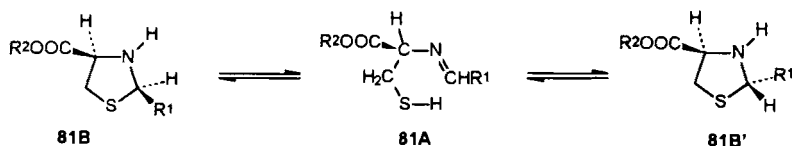
In neutral aqueous solution, 1-(3-aminopropyl)pyrroline exists predominantly as the bicyclic tautomer, whereas in acidic solution ( $\text{pD} < 4.5$ ), the *N*-protonation leads to ring opening [84ACS(B)526].



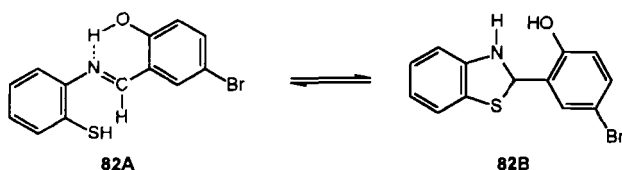
### C. ADDITION OF AN SH GROUP

#### 1. *N*-Mercaptoalkyl and *N*-Mercaptoaryl Imines

The epimerization at C(2) of the diastereomeric thiazolidines **81B**  $\rightleftharpoons$  **81B'** proceeds in neutral or basic medium via an intermediate with the open-chain structure **81A** (79JA427; 82OMR138). Direct <sup>1</sup>H-NMR spectroscopic evidence has been obtained (75T907) in favor of the presence of the open-chain anion in alkaline solution.



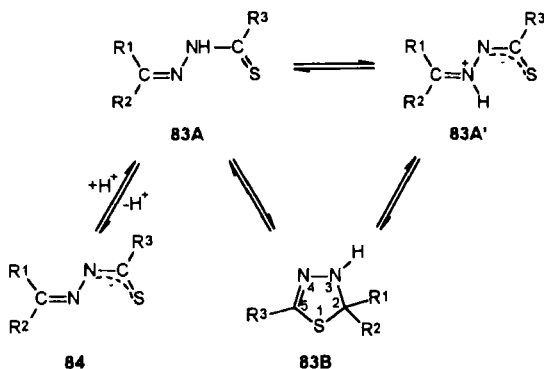
The equilibrium **82A**  $\rightleftharpoons$  **82B** was proved (88TL5427; 90T6545) in solutions of 2-(5-bromo-2-hydroxyphenyl)benzothiazoline. In CDCl<sub>3</sub>,  $K_T = 24.6$ , and in (CD<sub>3</sub>)<sub>2</sub>SO,  $K_T = 24$  (<sup>1</sup>H-NMR). The open-chain tautomer **82A** is stabilized by an intramolecular hydrogen bond. Comparison of the quantitative data on the ring-chain tautomeric equilibria of 1,3-thiazolidines and 1,3-oxazolidines has led to the conclusion (90T6545) that the stability difference between the cyclic tautomers of 1,3-thiazolidine and 1,3-oxazolidine is about 10<sup>-4</sup>–10<sup>-6</sup> in favor of the sulfur-containing heterocycle. This means that the ring-chain tautomerism in 1,3-thiazolidines can be detected by NMR methods only in those rather rare systems containing additional structural factors that stabilize the open-chain tautomer.



## 2. Aldehyde and Ketone *N*-Thioacylhydrazones and Related Compounds

In comparison with the oxygen- or nitrogen-containing derivatives of similar structure, the most expressed tendency to the formation of cyclic tautomers by intramolecular SH group addition to the C=N bond is exhibited by aldehyde and ketone thioacylhydrazones [for a review, see (88KGS3)].

Aldehyde and ketone thiobenzoylhydrazones possess the cyclic 1,3,4-thiadiazoline structure **83B** ( $R^3 = \text{Ar}$ ), proved by  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectroscopy in nonpolar solvents and by mass spectrometry in the gas phase [80ZOR2237; 82JCS(CC)188; 82KGS904; 84ZOR169; 92CB1389]. For two derivatives ( $R^1 = \text{H}$ ;  $R^2 = 4\text{-MeOC}_6\text{H}_4$ ;  $R^3 = \text{Ph}$ ; and  $R^1 = R^2 = \text{Me}$ ;  $R^3 = \text{Ph}$ ), the equilibrium  $\mathbf{83A} \rightleftharpoons \mathbf{83B}$  was detected in  $\text{CD}_3\text{OD}$  solution, but the content of the open-chain tautomer **83A** does not exceed 7–10%. Through the protonation at N(4), these compounds maintain their cyclic structure. In alkaline medium, the anions of the open-chain structure **84** were formed.



Aldehyde and ketone thioacylhydrazones ( $R^3 = \text{H}$ , alkyl) exhibit ring-chain equilibrium more frequently (81KGS1569; 84ZOR169). In nonpolar solvents, the equilibrium  $\mathbf{83A} \rightleftharpoons \mathbf{83B}$  appears, but in polar aprotic solvents [ $(\text{CD}_3)_2\text{SO}$ ,  $(\text{CD}_3)_2\text{NCDO}$ ], the three-component equilibrium  $\mathbf{83A} \rightleftharpoons \mathbf{83A'} \rightleftharpoons \mathbf{83B}$  occurs (see Table XV).

As is obvious from the data in Table XV, an increase in the steric demands ( $R^3 = t\text{-Bu}$ ) or electron-withdrawing ability ( $R^3 = \text{Ph}$ ) of the substituent in the thiohydrazone moiety stabilizes the cyclic tautomer **83B**. Electron-donating or sterically bulky substituents  $R^1$  and  $R^2$  that decrease the electro-

TABLE XV  
PERCENTAGES OF THE TAUTOMERS AND EQUILIBRIUM CONSTANTS  
OF THIOACYLHYDRAZONES (**83**)<sup>a</sup>

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	$K_T = [B]/[A]$ in CDCl <sub>3</sub>	Percentage in (CD <sub>3</sub> ) <sub>2</sub> SO			[B]/[A + A']
				A	A'	B	
Ph	Ph	H	0	100	0	0	0
H	Ph	Me	0.28	85	15	0	0
Me	Ph	Me	0	—	—	—	—
Ph	Ph	Me	0	82	18	0	0
H	Ph	<i>t</i> -Bu	>30	—	—	—	>30
Me	Me	<i>t</i> -Bu	>30	—	—	—	>30
H	Ph	PhCH <sub>2</sub>	1.22	83	10	7	0.08
H	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	PhCH <sub>2</sub>	9	80	7	13	0.15
H	4-MeOC <sub>6</sub> H <sub>4</sub>	PhCH <sub>2</sub>	0.52	90	10	0	0
Me	Me	PhCH <sub>2</sub>	4.88	30	5	65	1.86
Me	<i>i</i> -Bu	PhCH <sub>2</sub>	0.79	55	25	20	0.25
Me	<i>t</i> -Bu	PhCH <sub>2</sub>	0.59	62	15	23	0.30
Me	Ph	PhCH <sub>2</sub>	0.14	66	26	8	0.09
Me	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	PhCH <sub>2</sub>	0.72	68	22	10	0.11
Me	4-MeOC <sub>6</sub> H <sub>4</sub>	PhCH <sub>2</sub>	0	67	32	0	0
Ph	Ph	PhCH <sub>2</sub>	0	55	45	0	0
H	4-MeOC <sub>6</sub> H <sub>4</sub>	Ph	>30	18	10	72	2.57
Me	Me	Ph	>30	5	0	95	19
Ph	Ph	Ph	>30	—	—	—	—

<sup>a</sup> Data from Zelenin *et al.* (84ZOR169). Determined by <sup>1</sup>H-NMR at 25°C 72 hours after dissolution.

philicity or steric accessibility of the C=N group carbon atom stabilize the open-chain tautomer **83A**.

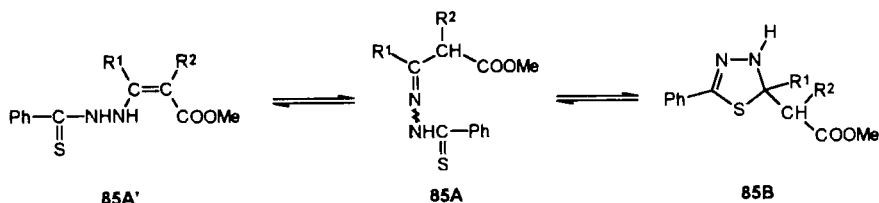
For D-glucose thiobenzoylhydrazone, an equilibrium mixture was observed (92KGS571; 93ZOR278) that contains not only the open-chain and 1,3,4-thiadiazoline (like **83B**) tautomers, but also 1-thiobenzoylhydrazinopyranose.

Products with cyclic the 1,3,4-thiadiazoline structure were obtained (81ZOR589; 81ZOR1561) in the reactions of isatin and 1-alkylisatins with thiobenzhydrazide.

Monothiobenzoylhydrazones of butane-2,3-dione and of benzil exist as stable 1,3,4-thiadiazolines **83B** (R<sup>1</sup> = Me, Ph; R<sup>2</sup> = MeCO, PhCO; R<sup>3</sup> = Ph), whereas the corresponding phenylacetylhydrazones (R<sup>3</sup> = PhCH<sub>2</sub>) produce equilibrium mixtures **83A** ⇌ **83B** in solution (83KGS769).



The reactions of methyl 3-oxobutanoate or its 2-alkyl-substituted derivatives with thiobenzhydrazide lead to the 1,3,4-thiadiazolines **85B** ( $R^1 = \text{Me}$ ;  $R^2 = \text{H, Me, Et, } i\text{-Pr}$ ) (83KGS1048). An increase in the steric demands of the substituent  $R^2$  destabilizes the cyclic tautomer; and when  $R^2 = i\text{-Pr}$ , the equilibrium mixture **85A**  $\rightleftharpoons$  **85B** ( $R^1 = \text{Me}$ ) appears in  $(\text{CD}_3)_2\text{SO}$  solution. This mixture contains *ca.* 10% of the open-chain tautomer **85A**.



Thiobenzoylhydrazones of 2-methoxycarbonylcyclanones exhibit an equilibrium involving the enhydrazine open-chain tautomer: **85A'**  $\rightleftharpoons$  **85B** [ $R^1, R^2 = (\text{CH}_2)_n$ ;  $n = 3, 4$ ]. In  $\text{CCl}_4$  solution, when  $n = 3$ ,  $K_T = [\text{B}]/[\text{A}'] = 0.96$ ; when  $n = 4$ ,  $K_T = 2.85$ . Increasing solvent polarity displaces the equilibrium toward the enhydrazine tautomer **85A'**.

For the 1,3-diketone and 3-oxoaldehyde monothioacylhydrazones, two competitive pathways of intramolecular cyclization are regarded as possible: addition of the SH group to the  $\text{C}=\text{N}$  bond to yield 1,3,4-thiadiazoline **86B**, and addition of the NH group to the  $\text{C}=\text{O}$  bond to yield pyrazoline **86C**. As a result, a three-component equilibrium **86B**  $\rightleftharpoons$  **86A**  $\rightleftharpoons$  **86C** could be detected. Zelenin and co-workers (81ZOR2451) have observed such a phenomenon, but without detectable amounts of the open-chain tautomer **86A**. Pentane-2,4-dione monothiobenzoylhydrazone was isolated in the solid state as the pyrazoline **86C** ( $R^1 = R^2 = \text{Me}$ ;  $R^3 = \text{H}$ ). Data from  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR and IR spectroscopy indicate that the equilibrium **86B**  $\rightleftharpoons$  **86C** is rapidly attained in solution. In  $\text{CDCl}_3$ ,  $K_T = [\text{C}]/[\text{B}] = 0.45$ ; in  $\text{CCl}_4$ ,  $K_T = 0.64$ ; in  $\text{CD}_3\text{OD}$ ,  $K_T = 0.82$ ; and in  $(\text{CD}_3)_2\text{NCDO}$ ,  $K_T = 1.04$ . In a more detailed investigation (84ZOR180), the four-component equilibrium **86A**  $\rightleftharpoons$  **86A'**  $\rightleftharpoons$  **86B**  $\rightleftharpoons$  **86C** was observed in  $(\text{CD}_3)_2\text{SO}$ . Thiobenzoylhydrazones of aroylacetaldehydes exist only as the 1,3,4-thiadiazolines **86B** ( $R^1 = R^3 = \text{H}$ ;  $R^2 = 4\text{-XC}_6\text{H}_4$ ,  $\text{X} = \text{H, MeO, NO}_2$ ) in the solid state and in solution (83ZOR1875). Thiobenzoylhydrazones of aroylacetones possess the same structure **86B** ( $R^1 = \text{Me}$ ;  $R^2 = 4\text{-XC}_6\text{H}_4$ ;  $R^3 = \text{H}$ ) in the solid state. In nonpolar solvents ( $\text{CDCl}_3$ ), the rapidly reached equilibrium **86B**  $\rightleftharpoons$  **86C** was observed (see Table XVI). The introduction of an electron-withdrawing substituent X onto the aryl group ( $R^2 = 4\text{-XC}_6\text{H}_4$ ) shifts the equilibrium in favor of the pyrazoline tautomer **86C** owing to the increased  $\text{C}=\text{O}$  group electrophilicity in the open-chain tautomer **86A**. In  $(\text{CD}_3)_2\text{SO}$

TABLE XVI  
PERCENTAGES OF TAUTOMERS OF  
THIOBENZONYLHYDRAZONES OF AROYLACETONES  
(**86**,  $R^1 = \text{Me}$ ;  $R^2 = 4\text{-XC}_6\text{H}_4$ ;  $R^3 = \text{H}$ ) AND  
EQUILIBRIUM (**86B**  $\rightleftharpoons$  **86C**) CONSTANTS<sup>a</sup>

X	[C]/[B] in CDCl <sub>3</sub>	Percentage in (CD <sub>3</sub> ) <sub>2</sub> SO		
		B	C	A'
Me <sub>2</sub> N	0	81	—	9
MeO	0.09	78	—	22
Me	0.12	69	2	29
H	0.20	64	5	31
Br	0.30	51	7	42
NO <sub>2</sub>	2.20	23	24	53

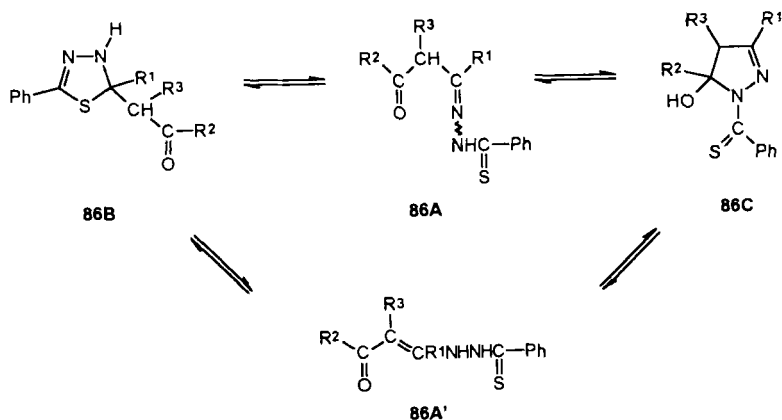
<sup>a</sup> Data from Yakimovich *et al.* (83ZOR1875). Determined by <sup>1</sup>H-NMR at 30°C.

solution, the three-component equilibrium **86A**  $\rightleftharpoons$  **86A'**  $\rightleftharpoons$  **86C** exists (Table XVI). The influence of substituent X ( $R^2 = 4\text{-XC}_6\text{H}_4$ ) on this equilibrium was evaluated by using equations correlating the equilibrium constants with the  $\sigma$  constants of substituent X (see Table XVII). The introduction of an electron-withdrawing substituent X shifts the general ring-chain equilibrium  $K_{T_1} = [\text{B} + \text{C}]/[\text{A}']$  with the equilibrium  $T_2$  (**A'**  $\rightleftharpoons$  **B**) in favor of the open-chain tautomer **86A'** ( $\rho < 0$  for both cases). Simultaneously, the equilibria  $T_3$  (**A'**  $\rightleftharpoons$  **C**) and  $T_4$  (**B**  $\rightleftharpoons$  **C**) are shifted in favor of the pyrazoline tautomer **86C** ( $\rho > 0$ ). However, there are no indications of the presence of the hydrazone tautomer **86A** in the <sup>1</sup>H-NMR spectra (83ZOR1875).

TABLE XVII  
CORRELATION PARAMETERS OF EQUILIBRIUM  
CONSTANTS OF THIOBENZONYLHYDRAZONES OF  
AROYLACETONES (**86**,  $R^1 = \text{Me}$ ;  $R^2 = 4\text{-XC}_6\text{H}_4$ ;  
 $R^3 = \text{H}$ ) WITH  $\sigma$  CONSTANTS OF SUBSTITUENTS<sup>a</sup>

Equilibrium constant	$\log(K_T)_0$	$\rho$	$r$	$n$
$K_{T_1} = [\text{B} + \text{C}]/[\text{A}']$	0.37	-0.66	0.98	6
$K_{T_2} = [\text{B}]/[\text{A}']$	0.29	-0.85	0.99	6
$K_{T_3} = [\text{C}]/[\text{A}']$	-0.95	0.79	0.97	4
$K_{T_4} = [\text{C}]/[\text{B}]$	-1.20	1.58	0.97	4

<sup>a</sup> Data from Yakimovich *et al.* (83ZOR1875). For X, see Table XVI.



In a large series of symmetrically (**86**,  $R^1 = R^2$ ) or unsymmetrically ( $R^1 \neq R^2$ ) substituted 1,3-diketone thiobenzoylhydrazones (84ZOR180), the following regularities of the influence of the substituents  $R^1$ ,  $R^2$ , and  $R^3$  on the equilibria have been established (see Table XVIII). Only a two-component equilibrium **86B**  $\rightleftharpoons$  **86C** is observed in nonpolar solvents ( $\text{CDCl}_3$ ), without any detectable amount of the open-chain tautomers. Increase of the  $\text{C}=\text{N}$  bond reactivity due to the steric or electronic influence of the substituent at this bond ( $R^1 = \text{H}$ ,  $\text{CF}_3$ ,  $\text{COOMe}$ ) and increase of the steric demands of the substituent at the  $\text{C}=\text{O}$  bond ( $R^2 = t\text{-Bu}$ ) lead, as expected, to complete predominance of the 1,3,4-thiadiazoline tautomer **86B**; i.e., the above-mentioned structural factors act in favor of intramolecular addition only to the  $\text{C}=\text{N}$  bond. For the derivatives of symmetrically substituted 1,3-diketones, the amount of pyrazoline **86C** increases with increase of the steric demands of the substituents  $R^1 = R^2$  in the series  $\text{Me} < \text{Et} < i\text{-Pr}$ , but for  $R^1 = R^2 = t\text{-Bu}$  the amount decreases. The introduction of the  $\alpha$ -alkyl substituent into the 1,3-diketone moiety and the increase of its steric demands in the sequence  $R^3 = \text{Me} < \text{Et} < i\text{-Pr} < \text{PhCH}_2$  stabilize the cyclic tautomer (i.e., **86C**) whose  $R^3$  substituent is on the ring carbon atom. These regularities also hold for solutions in  $(\text{CD}_3)_2\text{SO}$ , although the open-chain tautomers **86A** and **A'** have been detected in some cases (see Table XVIII). The open-chain enhydrazine tautomer **86A'** appears in the equilibrium for the *t*-butyl derivatives **86** ( $R^2 = t\text{-Bu}$ ;  $R^3 = \text{H}$ ), and its amount decreases with increase of the steric demands of substituent  $R^1 = \text{Me} < \text{Et} < i\text{-Pr}$ . Further increase of the bulk of this substituent ( $R^1 = t\text{-Bu}$ ) leads to the total disappearance of the enhydrazine tautomer **86A'**, but the open-chain hydrazone tautomer **86A** ( $R^1 = R^2 = t\text{-Bu}$ ;  $R^3 = \text{H}$ ) was detected first in this series.

TABLE XVIII  
PERCENTAGES OF TAUTOMERS OF 1,3-DIKETONE THIOMBENZOYLHYDRAZONES (**86**) AND  
EQUILIBRIUM **86B**  $\rightleftharpoons$  **86C** CONSTANTS<sup>a</sup>

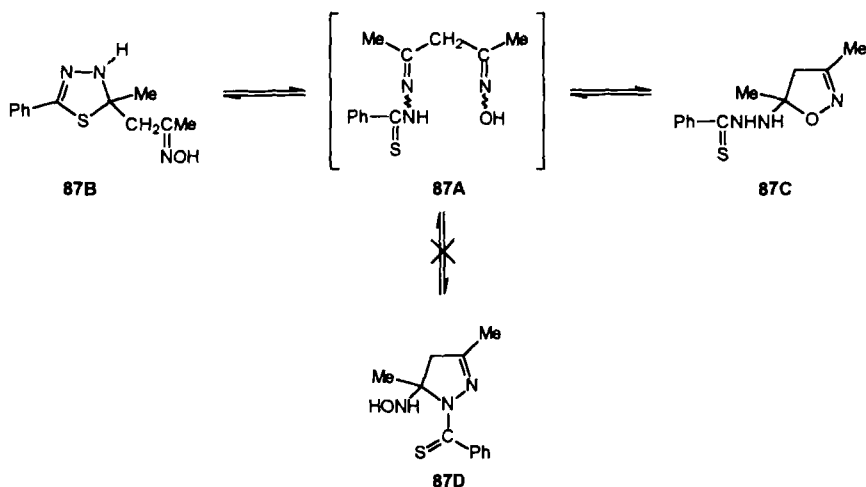
R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	[C]/[D] in CDCl <sub>3</sub>	Percentage in (CD <sub>3</sub> ) <sub>2</sub> SO			
				A	B	C	A'
H	<i>t</i> -Bu	H	0	—	100	—	—
Me	Me	H	2.23	—	50	50	—
Me	<i>t</i> -Bu	H	0	—	85	—	15
CF <sub>3</sub>	Me	H	0	—	—	—	—
Et	Et	H	2.85	—	35	65	—
Et	<i>t</i> -Bu	H	0	—	90	—	10
<i>i</i> -Pr	<i>i</i> -Pr	H	>30	—	—	100	—
<i>i</i> -Pr	<i>t</i> -Bu	H	0	—	95	—	5
<i>t</i> -Bu	<i>t</i> -Bu	H	2.13	15	55	30	—
COOMe	<i>t</i> -Bu	H	0	—	100	—	—
Me	Me	Me	2.03	—	—	—	—
Me	Me	Et	2.57	—	—	—	—
Me	Me	<i>i</i> -Bu	3.0	—	—	—	—
Me	Me	PhCH <sub>2</sub>	4.26	—	—	—	—

<sup>a</sup> Data from Zelenin *et al.* (84ZOR180). Determined by <sup>1</sup>H-NMR.

The data in Tables XVI and XVIII reveal a general tendency for the 1,3,4-thiadiazoline tautomer **86B** to predominate in the series of 1,3-diketone and 3-oxoaldehyde thiobenzoylhydrazones. The increased stability of the tautomer **86B** is attributable to the greater nucleophilicity of the sulfur atom as compared with that of nitrogen, and to the lower strain of the ring containing the sulfur atom. As can be foreseen (see 84ZOR169), pentane-2,4-dione thiophenylacetylhydrazone exists as stable 5-hydroxy-2,4-dimethyl-1-thiophenylacetyl-2-pyrazoline (84ZOR180).

Another type of ring-chain-ring tautomerism has been observed (85KGS1001) for pentane-2,4-dione oxime thiobenzoylhydrazone **87**. Whereas a four-component equilibrium involving three different heterocyclic tautomers (**87B**, **C**, **D**) is conceivable, only two components (**87B**, **C**) were detected. Compound **87** exists as the isoxazoline tautomer **87C** in the solid state and in nonpolar solvents (CDCl<sub>3</sub>). Data from <sup>1</sup>H- and <sup>13</sup>C-NMR reveal that the equilibrium **87B**  $\rightleftharpoons$  **87C** appears in polar solvents such as CD<sub>3</sub>OD, (CD<sub>3</sub>)<sub>2</sub>NCDO, (CD<sub>3</sub>)<sub>2</sub>SO, and C<sub>5</sub>D<sub>5</sub>N. There are no indications of the presence of the third cyclic tautomer **87D** in the NMR spectra.

The tautomerism exhibited by **87** is another example of "ring-ring tautomerism" (81ZOR2451; for a review, see 92KGS851) because the open-chain tautomer could not be detected by means of <sup>1</sup>H- and <sup>13</sup>C-NMR

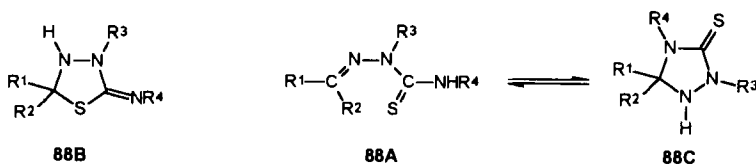


spectroscopy. The investigations of such equilibria provide valuable information on the relative stabilities of different heterocyclic systems. However, it is clear that these transformations may proceed only through the open-chain tautomer. Thus we are actually dealing here with two (or more) competitive ring-chain tautomeric systems involving the same open-chain tautomer, albeit in such a low concentration that its detection often falls below the sensitivity of the investigation methods used. Such phenomena are well known in the chemistry of monosaccharides, where the use of more sensitive methods (84MI2; 87JA3168) has led to the successful determination of very low concentrations of open-chain tautomer.

### 3. Aldehyde and Ketone Thiosemicarbazones

In an early investigation [70LA(731)142], it was supposed that the equilibrium  $\mathbf{88A} \rightleftharpoons \mathbf{88B}$  exists in acidic solutions of aldehyde and ketone 2-substituted thiosemicarbazones [for a detailed review, see (93KGS991)]. Later, it was shown (79JHC1273) that acetone thiosemicarbazone  $\mathbf{88}$  ( $R^1 = R^2 = \text{Me}$ ;  $R^3 = R^4 = \text{H}$ ) and its 2-methyl ( $R^3 = \text{Me}$ ) and 4-methyl ( $R^4 = \text{Me}$ ) derivatives exist as open-chain isomers in  $(\text{CD}_3)_2\text{SO}$  solution, but as cyclic isomers  $\mathbf{88B}$  in  $\text{CF}_3\text{COOD}$ . According to this investigation, the 2,4-dimethyl-substituted derivative exists solely as the cyclic tautomer  $\mathbf{88B}$  ( $R^1 = R^2 = R^3 = R^4 = \text{Me}$ ) in both of these solvents.

Detailed investigation [87DOK(296)1133] showed that the open-chain isomer  $\mathbf{88A}$  ( $R^1 = R^2 = R^3 = R^4 = \text{Me}$ ) is formed at the beginning of the



reaction of acetone with 2,4-dimethylthiosemicarbazide. <sup>15</sup>N-NMR data show that this open-chain isomer readily transforms into the cyclic 1,2,4-triazolidine-3-thione **88C**.

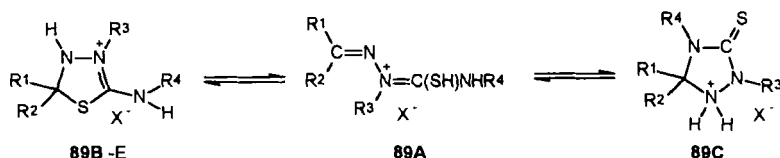
Investigation (92KGS1689; 93T1257) of a large series of variously substituted aldehyde and ketone thiosemicarbazones indicates that, in general, the aldehyde thiosemicarbazones exist as open-chain isomers **88A** (R<sup>1</sup> = H; R<sup>2</sup> = Me, XC<sub>6</sub>H<sub>4</sub>; R<sup>3</sup> = H, Me; R<sup>4</sup> = H, Me, Et, PhCH<sub>2</sub>) in the solid state and in solution, independently of the presence of alkyl substituents in the thiosemicarbazide moiety (R<sup>3</sup>, R<sup>4</sup>) and of the character of the substituent X in the aryl group (when R<sup>2</sup> = XC<sub>6</sub>H<sub>4</sub>). In the gas phase, the presence of the cyclic isomer was detected by means of mass spectrometry. The introduction of an electron-withdrawing substituent X onto the aryl group (R<sup>3</sup> = XC<sub>6</sub>H<sub>4</sub>) increases the amount of the cyclic tautomer **88C** in the gas phase. *N*-Unsubstituted thiosemicarbazones of acetophenone and its aryl-substituted derivatives **88** (R<sup>1</sup> = Me; R<sup>2</sup> = XC<sub>6</sub>H<sub>4</sub>; R<sup>3</sup> = R<sup>4</sup> = H) also possess the open-chain structure, but the introduction of an electron-withdrawing substituent onto the aryl group, e.g., X = 4-NO<sub>2</sub>, allows detection of the presence of the cyclic tautomer **88C** in (CD<sub>3</sub>)<sub>2</sub>SO solution.

There is an exception in the series of arenecarbaldehyde *N*-unsubstituted thiosemicarbazones (92KGS1689). The freshly prepared solution of 2-chloro-6-nitrobenzaldehyde thiosemicarbazone in (CD<sub>3</sub>)<sub>2</sub>SO contains a mixture of the isomers **88A** and **88C**. However, on storage or heating of the solution, the ring opening **88C** → **88A** takes place. It may be presumed that the presence of two *o,o'*-substituents in the aryl group hinders the conjugation Ar-C=N on steric grounds, which slightly destabilizes the open-chain tautomer **88A**.

In contrast with the aldehyde derivatives, ketones reacting with 2-methyl- or 2,4-dialkylthiosemicarbazides form stable 1,2,4-triazolidine-3-thiones **88C** (R<sup>1</sup> = Me; R<sup>2</sup> = Me, Et, Ph; R<sup>3</sup> = Me, Et, PhCH<sub>2</sub>; R<sup>4</sup> = H, Me, Et, PhCH<sub>2</sub>), which existing as single isomers in neutral solution, as confirmed (93T1257) by <sup>1</sup>H-, <sup>13</sup>C-, and <sup>15</sup>N-NMR data. These cyclic isomers **88C** are significantly stabilized by the presence of methyl or, generally, alkyl substituents at N(2) and N(4) (R<sup>3</sup>, R<sup>4</sup> in **88**) in the thiosemicarbazide moiety.

By protonation of these 1,2,4-triazolidine-3-thiones **88C** on treatment with trifluoroacetic or other strong acid in CDCl<sub>3</sub> solution, the cations **89C**

( $X = CF_3COO$ ) were formed; but within minutes to hours, they underwent quantitative isomerization (recyclization) to 1,3,4-thiadiazolidin-2-iminium cations **89B**. The same cations were formed from the open-chain aldehyde thiosemicarbazones in trifluoroacetic acid solution. Deprotonation of the salts **89B** with  $C_5D_5N$  yielded the open-chain thiosemicarbazones **88A** and not the cyclic isomers **88B**. The open-chain isomers of ketone 2-methyl- or 2,4-dialkylthiosemicarbazones obtained in this way (**89B**  $\rightarrow$  **88A**) are unstable and readily cyclize into **88C** when their solutions are stored or when they undergo a recrystallization or thin-layer chromatography procedure.



*N*-Unsubstituted and 4-methylthiosemicarbazones of arenecarbaldehydes and acetophenones **88A** ( $R^1 = H, Me$ ;  $R^2 = XC_6H_4$ ;  $R^3 = H$ ;  $R^4 = H, Me$ ) in trifluoroacetic acid solution exhibit two-component equilibrium mixtures **89A**  $\rightleftharpoons$  **89B** (92KGS1689). For 4-methyl derivatives ( $R^4 = Me$ ), two fixed conformers ( $C_{(2)}$ -NHR<sup>4</sup> bond rotamers) of the cyclic tautomer **89B** (*E* and *Z*) were detected. The equilibrium **89A**  $\rightleftharpoons$  **89B** is rather insensitive to the nature of the substituent  $X$  ( $R^2 = XC_6H_4$ ). On passing from the aromatic aldehyde to the acetophenone derivatives, the equilibrium amount of the cyclic tautomer **89B** increases. The cyclic protonated form of 2-chloro-6-nitrobenzaldehyde thiosemicarbazone could not be detected at all. It would be of interest to test the thiosemicarbazones of other 2,6-disubstituted benzaldehydes. Recently, it has been found (94KGS119) that the protonated cinnamic aldehyde thiosemicarbazone **89A** ( $R^1 = PhCH=CH$ ,  $R^2 = R^3 = R^4 = H$ ) likewise does not form the cyclic tautomer **89B** in trifluoroacetic acid solution.

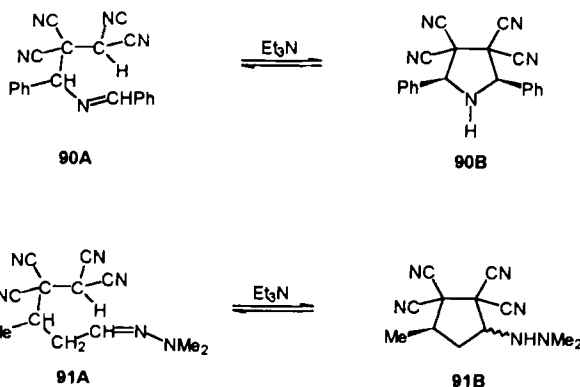
*N*-Unsubstituted and 4-alkylthiosemicarbazones of aliphatic aldehydes **88** ( $R^1 = R^3 = H$ ;  $R^2 = Me, Et, i\text{-}Pr$ ;  $R^4 = H, Me, PhCH_2, Ph$ ) exhibit only the three-component (or four-component when  $R^4 \neq H$ ) equilibrium **89B** (*E* and *Z*, when  $R^4 \neq H$ )  $\rightleftharpoons$  **89A**  $\rightleftharpoons$  **89C** in trifluoroacetic acid solution (93T5327). The tautomer **89B** (70–90%) prevails in the equilibrium, particularly at higher dilution. The contents of the tautomers **89A** and **89C** are roughly equal, *ca.* 5–10%. Replacement of an alkyl substituent  $R^2$  by an aryl group ( $R^2 = 4\text{-}MeOC_6H_4$ ) leads to total disappearance of the tautomer **89C**. Change from an aliphatic aldehyde to an acetone thiosemicarbazone or introduction of an alkyl substituent at N(2) ( $R^3 = \text{alkyl}$ ) stabilizes the 1,3,4-thiadiazoline tautomer **89B**.

The recyclization **88C**  $\rightarrow$  **89B** was found to be a general reaction of thiosemicarbazones in acidic media (93T1257, 93T5327). A similar recyclization was observed (90KGS1260) on dissolution of pentane-2,4-dione and dibenzoylmethane 2-methyl- and 2,4-dimethylthiosemicarbazones **88** ( $R^1 = \text{MeCOCH}_2$ ; and  $R^2 = \text{Me}$ ;  $R^1 = \text{PhCOCH}_2$ ;  $R^2 = \text{Ph}$ ;  $R^3 = \text{Me}$ ;  $R^4 = \text{H, Me}$ ) in trifluoroacetic acid.

#### D. ADDITION OF A CH GROUP

An important condition for reversible C—H group addition to the C=N bond is the presence of electron-withdrawing substituents on a carbon atom, which increases the acidity of the C—H group.

Through the use of IR spectroscopy, the equilibria **90A**  $\rightleftharpoons$  **90B** and **91A**  $\rightleftharpoons$  **91B** were detected [90DOK(313)110] under the conditions of basic catalysis [2% (Et)<sub>3</sub>N in dioxane solution]. Two cyano groups and the C(CN)<sub>2</sub> group increase the acidity of the C—H group. In the last equilibrium, two epimers of **91B** were detected.



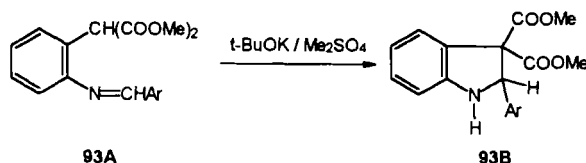
A shift of the equilibrium **92A**  $\rightleftharpoons$  **92B** in favor of the cyclic tautomer was observed by means of IR and <sup>1</sup>H-NMR spectroscopy (88AKZ385) in nonpolar solvents (CCl<sub>4</sub>, CDCl<sub>3</sub>) for alkylidene hydrazides of cyanoacetic





acid **92** ( $R^1 = R^2 = \text{Me}$  or  $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ). For the mass-spectrometric investigations of the equilibrium **92A**  $\rightleftharpoons$  **92B** in the gas phase, see (95KG1525).

In the presence of a strong basis catalyst (*t*-BuOK in Me<sub>2</sub>SO), the equilibrium of 2-arylideneaminophenyl malonic esters **93A**  $\rightleftharpoons$  **93B** [Ar = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 2,4-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 3,4,5-(MeO)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>] was completely shifted (isomerization) in favor of the cyclic tautomer (83JOC2468).

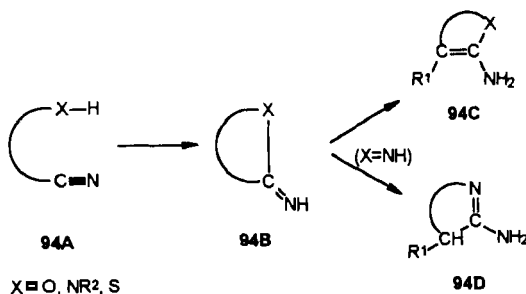


### III. Intramolecular Reversible Addition Reactions to Other Groups

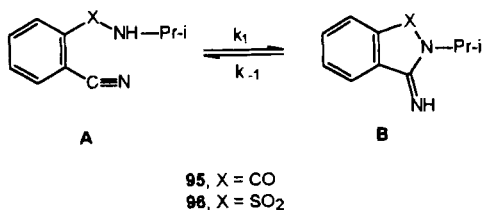
#### A. ADDITION TO THE $\text{C}\equiv\text{N}$ GROUP

Two monographs devoted entirely to cyclization reactions involving the intramolecular addition of C—H, O—H, S—H (85MI1), or N—H groups (87MI1) to the  $\text{C}\equiv\text{N}$  bond have been published in Russian. However, the main interest of the authors of these books was the synthetic utility of these intramolecular reactions.

The hydroxy-, amino-, or mercaptonitriles **94A** ( $X = \text{O}, \text{NR}, \text{SH}$ ) that have been isolated undergo cyclization to **94B** readily—and, in most cases, irreversibly—on heating in polar solvents, in the presence of acidic or basic catalysts, or upon melting. The iminoheterocycles **94B** often isomerize subsequently to amines **94C** or **94D**, shifting the double bond into the ring. Equilibria of the type **94A**  $\rightleftharpoons$  **94B** have rarely been observed.



In a comparative study (83KGS1635) of the ability of the  $\text{SO}_2\text{NHR}$  and  $\text{CONHR}$  groups to undergo intramolecular addition, the cyclization rates ( $k_1$ ) and ring-chain equilibrium constants were measured for *N*-isopropyl-2-cyanobenzamide (**95**) and benzenesulfonamide (**96**) in  $\text{CD}_3\text{OD}$  solution (Table XIX). The tabulated data demonstrate that the equilibrium  $\mathbf{95A} \rightleftharpoons \mathbf{95B}$  was shifted quantitatively (within the sensitivity limits of the  $^1\text{H-NMR}$  method) toward the cyclic tautomer during several days, whereas the equilibrium  $\mathbf{96A} \rightleftharpoons \mathbf{96B}$  was shifted in the opposite direction. However, the rate constant ( $k_1$ ) of the cyclization reaction  $\mathbf{96A} \rightarrow \mathbf{96B}$  is significantly higher than that of the cyclization  $\mathbf{95A} \rightarrow \mathbf{95B}$ . Thus, on the change from benzamide to benzenesulfonamide, the cyclic tautomer is destabilized. The rate-limiting step appears to be the deprotonation [see 80ZOR353; 81DOK(256)398], and the sulfonamides, which contain the more acidic  $\text{NH}$  group, need less activation energy for the cyclization than the carboxamides.



A slowly reached (in 1 day) equilibrium  $\mathbf{97A} \rightleftharpoons \mathbf{97B}$  was observed (86JOC2988) in solutions of (2-azaaryl(amino)methylenemalononitriles. The equilibrium state exhibits a very high dependence on the solvent used (Table XX), the equilibrium being strongly shifted toward the open-chain

TABLE XIX  
RING-CHAIN EQUILIBRIUM AND RATE CONSTANTS  
OF *N*-ISOPROPYL 2-CYANO BENZAMIDE (**95**) AND  
2-CYANO BENZENESULFONAMIDE (**96**)<sup>a</sup>

Equilibrium	$k_1 \times 10^4 \text{ s}^{-1}$	$k_{-1} \times 10^4 \text{ s}^{-1}$	$K$
<b>95A</b> $\rightleftharpoons$ <b>95B</b>	0.58	—	>50
<b>96A</b> $\rightleftharpoons$ <b>96B</b>	4.5 <sup>b</sup>	10.1	0.45
	4.2 <sup>c</sup>	9.2	0.46

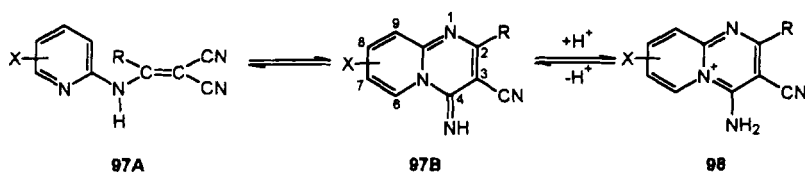
<sup>a</sup> Data from Valters *et al.* (83KGS1635). Determined by  $^1\text{H-NMR}$  in  $\text{CD}_3\text{OD}$  at  $25^\circ\text{C}$ . <sup>b</sup> The equilibrium is reached starting from the open-chain isomer **96A**. <sup>c</sup> The same, but starting from the cyclic isomer **96B**.

TABLE XX  
INFLUENCE OF SOLVENTS ON THE EQUILIBRIUM  
**97A**  $\rightleftharpoons$  **97B** (R = X = H) CONSTANTS<sup>a</sup>

Solvent	$K_T$
CDCl <sub>2</sub> -CDCl <sub>2</sub>	24
D <sub>2</sub> O	19
CDCl <sub>3</sub>	4
CD <sub>3</sub> NO <sub>2</sub>	4
CD <sub>3</sub> CN	1.6
CD <sub>3</sub> OD	1.5
(CD <sub>3</sub> ) <sub>2</sub> CO	0.39
(CD <sub>3</sub> ) <sub>2</sub> SO	0.05

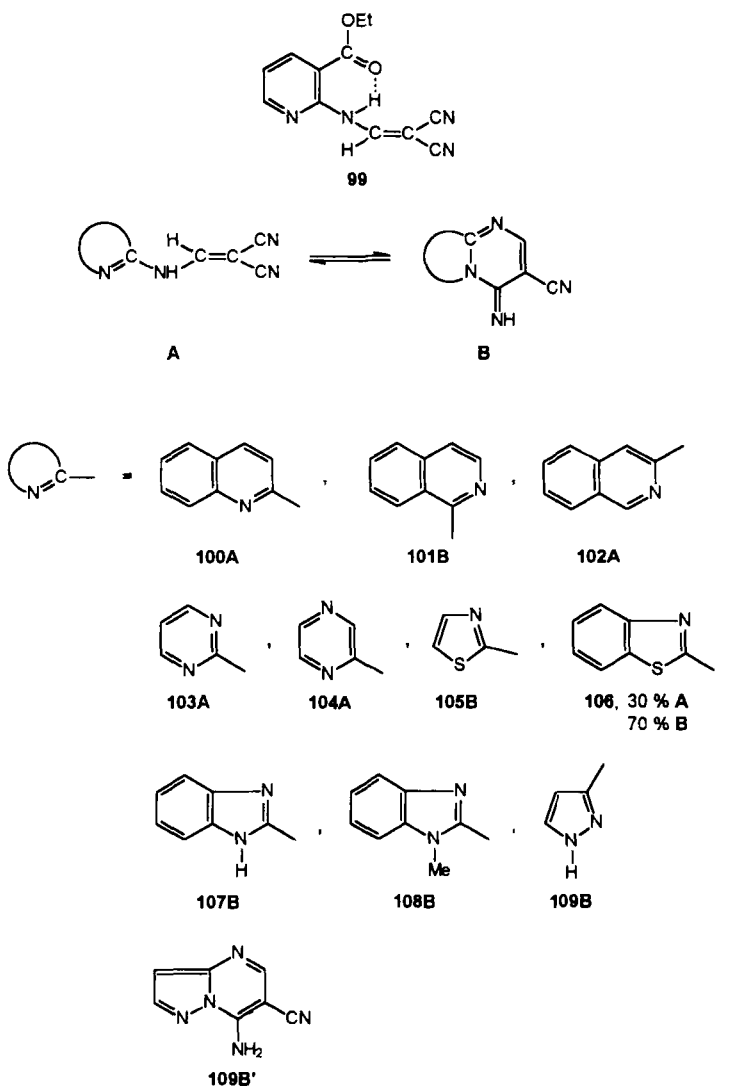
<sup>a</sup> Data from Podányi *et al.* (86JOC2988). Determined by <sup>1</sup>H-NMR at 30°C, 24 hours after the dissolution.

tautomer **97A** in polar proton-accepting solvents. Protonation, resulting in an aromatic pyrido[1,2-*a*]pyrimidinium cation **98**, stabilizes the cyclic structure.



The introduction of an alkyl or phenyl substituent at position 2 strongly stabilizes the cyclic tautomer **97B** (R = Me, Et, Pr, Ph; X = H), as is generally observed for the substituents in the chain between two interacting groups [Thorpe-Ingold effect; for a more recent discussion of this effect, see (90SL186; 94JA10789)]. No <sup>1</sup>H-NMR signals of the open-chain tautomer could be detected even at 100°C in C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub> solutions of the derivatives **97B** (R = Me, Ph; X = H). For 6-substituted 2-aminopyridine derivatives **97** (R = H, X = 6-Me or 6-COOEt; R = Me, X = 6-COOEt), the equilibrium is shifted fully in favor of the open-chain tautomer **97A** owing to an unfavorable nonbonding interaction between the substituent 6-X and the adjacent imino group in the cyclic tautomer **97B**. In the derivatives **97** substituted at position 7 or 8 (see formula **97B**), the methyl group increases the equilibrium amount of the cyclic tautomer, while electron-withdrawing groups (**97**; X = 7-COOEt, Cl, Br, 8-COOEt; always R = H) act in the opposite direction. This can be explained by the substituent effect on the pyridine

nitrogen atom basicity in the open-chain structure **97A**: an increase in this basicity stabilizes the cyclic tautomer owing to the electronic effect of the substituent. For the 9-methyl derivative **97B** ( $X = 9\text{-Me}$ ;  $R = \text{H}$ ), the cyclic tautomer predominates even in  $(\text{CD}_3)_2\text{SO}$  solution; this may be caused by the more unfavorable steric congestion of the substituents in the open-chain tautomer **95A**. In contrast, the derivative **99** exists as the open-chain tautomer, even in  $\text{CDCl}_3$ , stabilized by an intramolecular hydrogen bond.



This study (86JOC2988) was extended to a large series of compounds of similar structure, **100**–**109**.<sup>2</sup> The derivatives of 2-aminoquinoline **100**, 3-aminoisoquinoline **102**, 2-aminopyrimidine **103**, and 2-aminopyrazine **104** exist as open-chain tautomers in (CD<sub>3</sub>)<sub>2</sub>SO solution; but for the derivatives of 1-aminoisoquinoline **101** and of the five-membered  $\pi$ -electron-enriched heterocycles **105**–**109**, the cyclic tautomer predominates. The cyclic tautomers of the benzimidazole **107B** and pyrazole **109B** derivatives, containing an additional mobile hydrogen atom in the parent heterocycle moiety, are capable of further prototropic tautomerizations. Both the open-chain **109A** and the cyclic **109B'** isomers were isolated in the solid state, the latter existing in a structure containing an amino group formed after the isomerization **109B**  $\rightarrow$  **109B'**. On storage of a solution of the open-chain isomer **109A** in (CD<sub>3</sub>)<sub>2</sub>SO at ambient temperature, the slow isomerization **109A**  $\rightarrow$  **109B'** proceeds ( $k_1 = 1.1 \times 10^{-7} \text{ s}^{-1}$ ,  $\Delta G_{295}^\ddagger = 26.2 \text{ kcal/mol}$ ). This isomerization also takes place on attempted crystallization from ethanol or on melting.

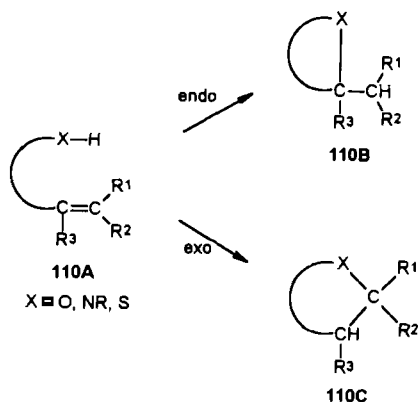
## B. ADDITION TO THE C=C AND C $\equiv$ C GROUPS

Many examples of the intramolecular addition of hydroxy, amino, or mercapto groups to C=C or C $\equiv$ C bonds are known to lead to the formation of a heterocycle [64QR211; 84JCS(P2)1259, 84JCS(P2)1269].

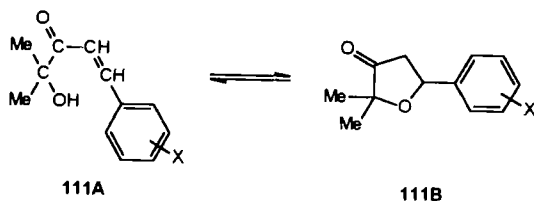
The kinetics and regiospecificity of these reactions have been extensively investigated with the aim of evaluating the utility and limitations of the Baldwin rules (83JA5090, 83MI1, 83T1013; 93ACR476). Depending on the size of the ring formed, on the substituents (R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> in **110**) on the ethylene or acetylene (86JOC4432) bond, on the structure of the connecting link, and on the character of the nucleophilic group XH, the intramolecular attack can proceed in two directions: *endo* and *exo*.

In most cases, the cyclization occurs irreversibly under acidic or basic conditions or on heating. However, there are examples of pH-dependent reversible intramolecular additions, too (84M101; 93KGS1139). The rather rare ring-chain equilibria are generally observed for derivatives containing multiple bonds of increased polarity (I-221) or in strong acidic or basic media. For instance, the equilibrium **111A**  $\rightleftharpoons$  **111B** was observed (83JA5090, 83TL2851; 90CJC1780) in trifluoroacetic acid solution. The

<sup>2</sup> The structure of the isomer shown is that of the compound found in (CD<sub>3</sub>)<sub>2</sub>SO solution.

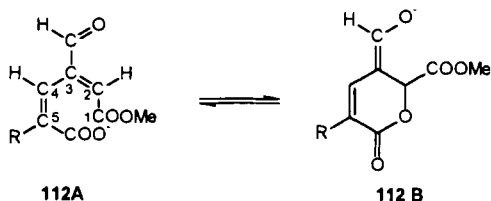


introduction of an electron-withdrawing substituent  $X$  shifts the equilibrium in favor of the cyclic tautomer ( $\rho = +0.4$ ), but slows down the ring closure.

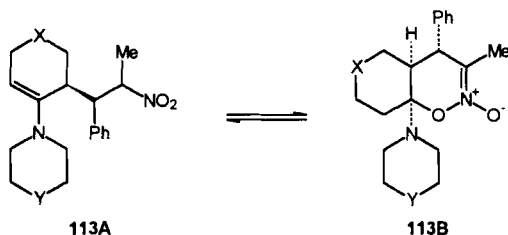


The equilibrium between open-chain and cyclic anions **112A**  $\rightleftharpoons$  **112B** ( $R = H$ ) was observed (89JOC1506) in basic solutions of the 1-monomethyl ester of (2*E*,4*Z*)-3,2,4-hexadienedioic acid. The ring closure is caused by addition of an intramolecular carboxylate anion to the polar  $C=C$  bond, with subsequent or simultaneous enolate anion formation. In the open-chain anion **112A**, the negative charge is concentrated in the carboxylate group, while in the cyclic anion **112B**, the charge is delocalized over an approximately planar backbone of seven atoms. Thus, the ring closure involves delocalization of the negative charge on going from the hard carboxylate **112A** to the soft enolate **112B** anion. Therefore, the hard open-chain anion is stabilized by solvents that are good hydrogen-bond donors (e.g., water), while the soft cyclic anion is stabilized by solvents of high polarizability. On the change from aqueous solution (all solutions contain potassium acetate as deprotonating agent) to *t*-butanol, the equilibrium constant, measured by means of UV spectroscopy, increases from  $K_T = 0.116$  to 12.5, which corresponds to a change in free-energy difference ( $\Delta G^\circ$ ) of 2.8 kcal/mol. Linear free-energy relationships with various solvent

polarity and polarizability parameters have been observed. Equilibrium constant measurements in mixtures of organic solvents with water show that the addition of even small amounts of an organic solvent to the aqueous solution increases the equilibrium amount of cyclic anion **112B** appreciably, presumably because of the specific interactions of the organic solvent molecules with the anion **112B**. Introduction of a methyl group or chlorine atom at position 5 (**112**, R = Me or Cl) shifts the equilibrium in favor of the open-chain anion.



The products of formal [4 + 2]-cycloaddition between enamines and (*E*)-1-phenyl-2-nitropropane display the ring-chain tautomeric equilibrium **113A**  $\rightleftharpoons$  **113B** (Table XXI), where the ring form is obtained by intramolecular nucleophilic addition of the NO<sub>2</sub> group to the enamine C=C bond (86CCA165) (see also I-222).



#### IV. Conclusions and Prospects

The data included in this review show that in many cases an increase in the sensitivity of the methods used in the investigation of ring-chain equilibria allows detection of more than one open-chain and/or cyclic tautomer in an equilibrium. The regularities governing simple two-component ring-chain equilibria are of rather limited value for such complicated tautomeric systems. Thus, for example, investigation of the equilibrium **75A'**  $\rightleftharpoons$  **75A**  $\rightleftharpoons$  **75B** (see **75A** in Part I [95AHC(64)251]), in which the amount of tautomer **75A** is often lower than the sensitivity limit of the method (NMR) used, shows that the enhydrazine-hydrazone equilibrium **75A'**  $\rightleftharpoons$  **75A** is controlled by the structural regularities, in contrast to the situation obtaining

TABLE XXI  
RING-CHAIN EQUILIBRIUM CONSTANTS OF  
1,2-OXAZINE *N*-OXIDES AND NITROOLEFINS  
(**113A**  $\rightleftharpoons$  **113B**)<sup>a</sup>

X	Y	$K_T$
CH- <i>t</i> -Bu	O	1
CH- <i>t</i> -Bu	CH <sub>2</sub>	0.7
NMe	O	3
NMe	CH <sub>2</sub>	1.9
O	CH <sub>2</sub>	1
S	CH <sub>2</sub>	5.7

<sup>a</sup> Data from Nitti *et al.* (86CCA165). Determined by <sup>1</sup>H-NMR in CDCl<sub>3</sub> solution at room temperature.

for the ring-chain equilibrium **75A**  $\rightleftharpoons$  **75B**. Consequently, it is difficult to predict the overall effect. An increase in the number of tautomers in an equilibrium (up to six at the present time) complicates this problem. The best way to simplify the investigation of such equilibria is to measure the separate equilibrium constants between each of the tautomeric pairs, but this is not always achievable experimentally.

The following general regularity holds strictly for all the equilibria discussed: "The more nucleophilic atom Q in the group Q-X (Q = O, NR, S; X = H, see formulas 1-4, Part I, Section I,A) and/or the more electrophilic the carbon atom of the group Y = Z (or Y  $\equiv$  Z), the more the equilibrium is shifted toward the cyclic tautomer." The criticism [93JCS(P2)635] that this simple generalization contains an incorrect transfer of the kinetic concepts into the field of thermodynamics is justified. However, another explanation based on the thermodynamic concepts [93JCS(P2)635] led to the same final conclusion.

With respect to the influence of the steric effects of substituents on interacting groups, it is difficult to draw general conclusions. Obviously, the most promising technique here is the application of the force-field calculations, which allows an estimation of the energy of the nonbonded steric interaction between the substituent and the remaining part of the molecule for the open-chain and cyclic tautomers separately.

We consider that there are at least two respects in which the information in this review will prove useful. First, the determination of the ring-chain equilibrium constants by means of spectroscopic methods readily yields information on the free-energy difference between the open-chain and cyclic tautomers. A purposeful selection of model compounds may reveal the general regularities of the influence of structural factors on this energy



difference. These regularities act similarly or nearly so in many significant chemical transformations of open-chain organic compounds via cyclic transition states, and of cyclic compounds via open-chain transition states or intermediates (82UK1374). Second, as pointed out by A. R. Katritzky in the preface of the book (I), many difficulties are encountered in determining the correct molecular structure of potentially tautomeric bifunctional compounds. Indeed, some of them have very small activation barriers, and even simple recrystallization leads to the isomeric transformation. Quite often, these compounds possess one structure in the solid state; but in solution, the equilibrium is strongly shifted toward a tautomer with another structure; for a more recent example, see [93JCS(P1)2615]. We hope that the information compiled here will help chemists to overcome these difficulties.

We consider it to be useful to carry out further investigations in the following directions:

- (1) a search for new pairs of functional groups whose intramolecular interaction leads to new ring-chain tautomeric systems;
- (2) the synthesis and investigation of polyfunctional potentially tautomeric compounds, leading to multi-component ring-chain (ring-chain-ring, etc.) equilibria;
- (3) a more quantitative elucidation of the influence of solvation effects on ring-chain equilibria; a search for methods allowing exact determination of ring-chain equilibrium constants in the gas phase;
- (4) quantitative determination of the influence of the connecting link structure on the ring-chain equilibrium constants for several pairs of interacting groups [as reported in (87JOC3821; 93JOC1967) for the pair OH and N=C];
- (5) a wider use of physical methods, e.g., full line shape analysis of NMR spectra, in order to broaden the currently rather sparse information on the activation barriers of several ring-chain equilibria;
- (6) the application of ring-chain tautomerism either in chemical transformation or in the development of potential pharmaceuticals.

## ADDENDUM

During the past year, investigations have been reported on the ring-chain tautomerism of 4-oxocarboxylic (95LA797) and 5-oxocarboxylic (95LA711) acids, 2-(2-quinolylcarbonyl)benzoyl chloride (95KG938), *o*-phthaloyl dichlorides (95JOC65888), reaction products of ninhidrin with 1,3-dicarbonyl compounds (95JHC33), *endo*-2-pivaloyl-*endo*-8-hydroxybicyclo[3.3.0]octane (95JOC7815), 5-hydroperoxy-5-alkoxyaldehydes forming seven-membered

hemiperacetals (95JOC4755), bromides of 2-(4-methoxybenzylamino)-1-(4-*R*-phenacyl)pyridinium (95KG644), and hydrazones of 1,3-diketones (94IJC(B)38; 95T11251).

Reviews have appeared that in part cover recent advances in the ring-chain tautomerism of the nitrogen-containing derivatives of 1,3-dicarbonyl compounds (95ZOB705); of the reaction products of alkenals, alkenones, and alkane-1,3-diones with hydrazines and hydroxylamines (95OPP519); and of other compounds [95H(41)1805; 95H(41)2057].

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# Palladium(0)-Catalyzed Allylation of Ambident Nucleophilic Aromatic Heterocycles

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## I. Introduction

Palladium(0)-catalyzed allylation of nucleophiles (the Tsuji–Trost reaction) is a versatile synthetic method that has gained immense popularity in recent years. Rarely applied to ambident nucleophilic aromatic heterocycles before 1991, the Tsuji–Trost reaction has been extensively used in the chemistry of these compounds since 1991. Two factors have played decisive roles in this increased interest in the Pd(0)-catalyzed allylation of such heterocyclic rings: one is that, unlike other alkylation procedures, the Pd(0)-catalyzed allylation can sometimes give the product of thermodynamic control when applied to ambident nucleophiles; and the second is that the Tsuji–Trost allylation has become one of the standard methods for synthesizing carbanucleosides, which are important antiviral compounds (93MI1, 93MI2). Of course, the double bond of an allylic system can be modified in different directions, thus adding versatility to the Tsuji–Trost reaction.

We include in Sections I,A and I,B some general features of the Tsuji–Trost reaction with comments on kinetic versus thermodynamic control in allylations and in alkylations in general. Then we review in Sections II, III, and IV all cases known to the authors of the application of the Tsuji–Trost reaction to ambident nucleophilic aromatic heterocycles. This leaves out of the review the allylation of such heterocyclic ambident nucleophiles as 2-piperidone and the like. By “aromatic,” we mean any heterocycle for which a tautomeric or mesomeric formula can be written that is aromatic in the normal structural sense of having  $4n + 2\pi$  electrons cyclically conjugated.

The retrieval of literature has presented difficulties. Frequently, the Tsuji–Trost method is used in multidisciplinary research to perform one step in the preparation of one compound. Because the object of such research is far from the Pd-catalyzed allylation, mention of the corresponding step is absent in the title, the abstract, and the key words. In this review, our intention has been to cover all the available literature, and we have made considerable efforts to do so. However, some readers may note that his or her work has been omitted. If so, this has been inadvertent and we apologize in advance. Moreover, we would be grateful if such omissions were communicated to us. The missing references will be included in future reviews.

### A. GENERAL FEATURES OF THE Pd(0)-CATALYZED ALLYLATION OF NUCLEOPHILES

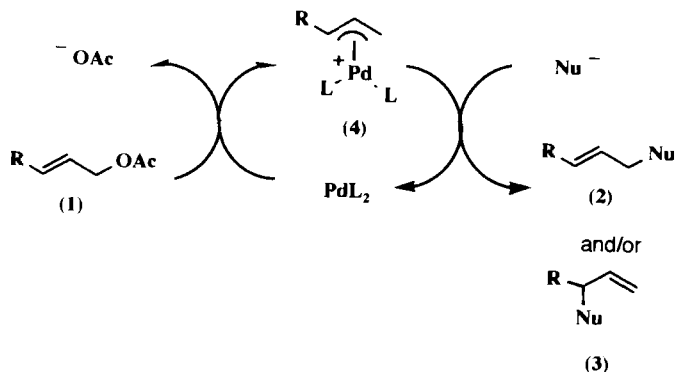
Palladium(0)-catalyzed allylation of nucleophiles (Tsuji–Trost reaction) has become a powerful synthetic method owing to its versatility, broad

scope, and facile experimental procedure. The Tsuji–Trost reaction is the displacement of a leaving group—most frequently acetoxy ( $-\text{OAc}$ ) in acetates or alkoxycarbonyloxy [ $-\text{OC}(=\text{O})-\text{OR}$ ] in mixed carbonates ( $\text{R} = \text{Me}$  or  $\text{Et}$ )—from an allylic framework by a nucleophile under  $\text{Pd}(0)$  catalysis. Excellent reviews have been published on the Tsuji–Trost reaction (91MI1; 92TA1089); therefore, we only mention here some essential features of the method.

The range of nucleophiles is very broad, embracing (i) nucleophiles based on carbon: stabilized enolates and related structures ( $\text{p}K_a$  of the conjugate acid 3–15), highly acidic hydrocarbons, ketone and ester enolates, organometallics  $\text{RM}$  ( $\text{M} = \text{Li}, \text{Mg}, \text{Zn}, \text{Tl}, \text{Al}, \text{Zr}, \text{Sn}, \text{B}$ ), and cyanide; (ii) nucleophiles based on silicon; (iii) nucleophiles based on nitrogen: amines, conjugate bases of amides, sulfonamides, as well as carbamates, azides, hydrazines, and hydroxylamine; (iv) nucleophiles based on phosphorus: triphenylphosphine, trialkyl phosphites, lithium salts of diphenylphosphine, and diphenylphosphine sulfide; (v) nucleophiles based on oxygen: alkoxides and phenoxides, hemiacetals, and triphenylsilanol; (vi) nucleophiles based on sulfur: arylsulfonates, trimethylsilylmercaptans, alkyl and arylmercaptans, and thioamides; (vii) nucleophiles based on hydrogen: equivalents of hydride ion (reducing agents).

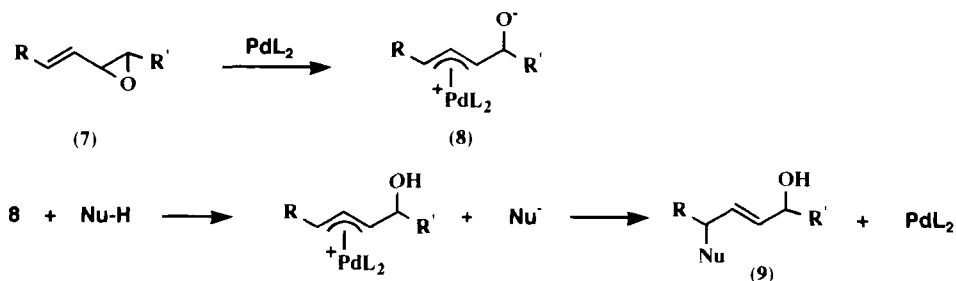
Palladium is generally introduced in catalytic amounts as the stable complexes  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{Pd}(\text{dba})_2$  ( $\text{dba} = \text{dibenzylideneacetone}$ ), frequently accompanied by a stabilizing phosphine [ $\text{PPh}_3$ ,  $\text{Ph}_2\text{P}-(\text{CH}_2)_n-\text{PPh}_2$ , or others], or as a form of  $\text{Pd}(\text{II})$  such as acetate, chloride, or acetylacetonate plus a phosphine. In the last case, the  $\text{Pd}(\text{II})$  is reduced *in situ* to the catalytically active  $\text{Pd}(0)$  species.

The accepted mechanism of the Tsuji–Trost reaction is as indicated in Scheme 1. The coordinatively unsaturated  $\text{PdL}_n$  ( $n < 4$  and possibly  $n = 2$ ) coordinates the double bond of the allylic system and displaces the



SCHEME 1

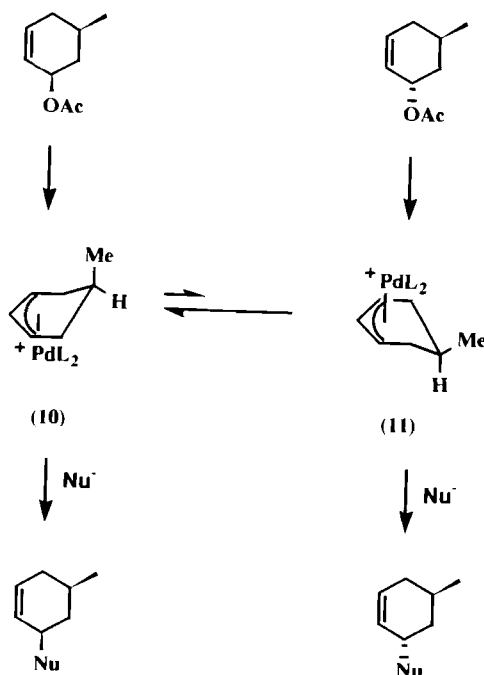
SCHEME 2



SCHEME 3

containing the terminal allylic carbon atoms. Almost without exception, the  $\text{PdL}_2$  attacks the allylic substrate from the side opposite to the leaving group, and therefore with inversion of configuration. The attack of the nucleophile occurs frequently by the side opposite to the palladium, and hence with a second inversion.

This stereochemistry results in overall retention (inversion + inversion) of configuration in the  $\text{Pd}(0)$ -catalyzed allylation of nucleophiles. This reten-



SCHEME 4



tion has been observed for stabilized carbanions, enolates, cyclopentadiene anion, arylsulfonates, thioalkoxides, thiophenoxides, the lithium salt of diphenylphosphine sulfide, and amines, as well as for all the compounds considered in this review for which stereochemical information is available.

Some nucleophiles (organometallics RM and hydride equivalents, featuring very weak conjugate acids) show a different stereochemical outcome, the attack of the nucleophile taking place at the palladium atom to form a neutral  $\eta^3$  complex. Reductive elimination—or, in other words, intramolecular delivery of the nucleophile to the allylic framework—occurs with retention of configuration. In short, the reactions with these types of nucleophiles occur with overall inversion (inversion + retention) of configuration.

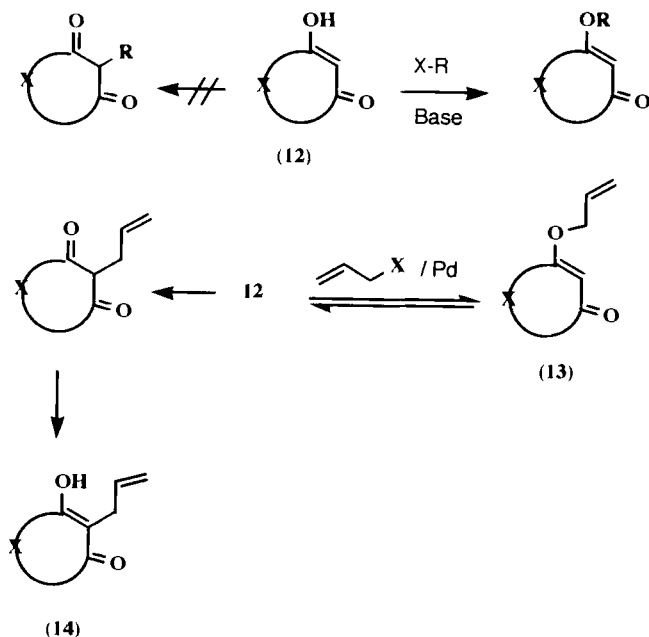
Although the most commonly used nucleophiles react by overall retention (inversion + inversion), an additional complication arises from the possibility of isomerization of the diastereoisomeric intermediates such as **10** and **11**.

## B. REACTIVITY OF HETEROCYCLIC AMBIDENT NUCLEOPHILES

An ambident (or polydent) heterocycle can react with electrophiles at two (or more) reacting sites. In general, alkylation with the usual combination of a base and an alkyl halide or any other good leaving group derivative is driven under kinetic control. One of the factors rendering the Pd(0)-catalyzed allylation procedure attractive is that, frequently, it can be driven under thermodynamic control, thereby occasionally affording an isomer not accessible by the reaction with alkyl halides in the presence of a base. For instance, the kinetic allylation of **12** gives **13**, in which Het-O— is, itself, a good leaving group in palladium chemistry. Therefore, **12** has a chance to alkylate at carbon under thermodynamic control to form **14** (Scheme 5). This is a case in which the nucleophilic atoms are oxygen and carbon, but other combinations are possible. Frequently, the regioselectivities achieved in the palladium-catalyzed allylations are higher than those observed by any other methods.

## C. SCOPE OF THE REVIEW

This review covers the Pd(0)-catalyzed allylations of aromatic ambident heterocyclic compounds, including all rings for which an aromatic tautomeric or resonance form can be written. Cases of C vs. O, C vs. N, N vs. O, and S vs. N allylation are discussed from all available viewpoints: regioselectivity, kinetic vs. thermodynamic control, mechanism, stereo-



SCHEME 5

chemistry, and targeted molecules. In other cases the N vs. N allylations will be reported [e.g., 4(5)-nitroimidazole], including a discussion of the effects of the substituents on the regioselectivity.

The review is organized by size of the ring and, within the size, by the nature and number of the heteroatom(s) contained in the ring. Fused heterocycles, as purine bases, are treated separately. Recently, Pd(0)-catalyzed allylation of purine bases and structurally related heterocycles has become one of the standard methods for preparing carbanucleosides having, in many cases, real antiviral activity. This is, of course, a subject of great interest.

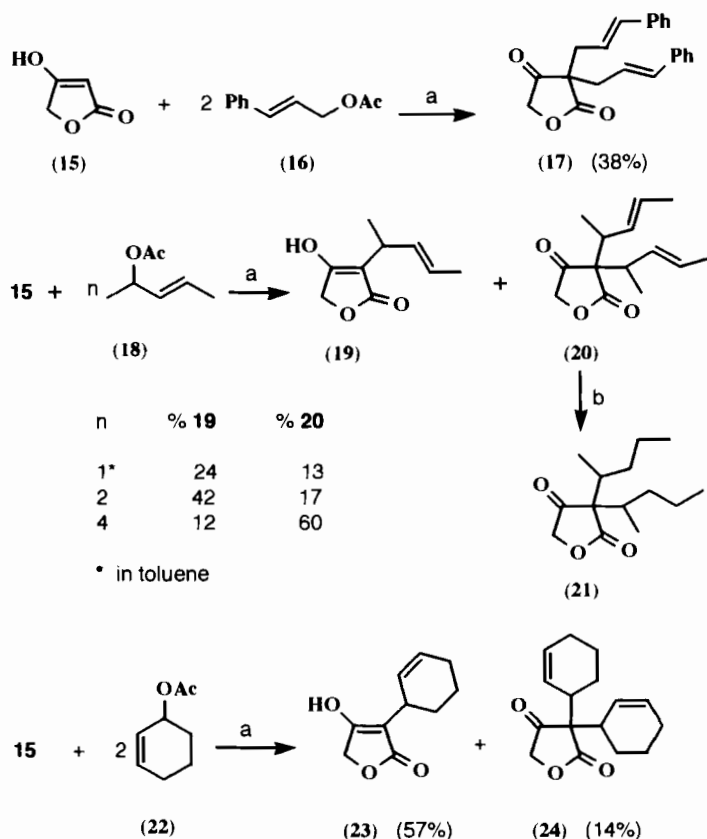
## II. Five-Membered Heterocyclic Rings

### A. OXYGEN-CONTAINING RINGS

#### 1. Tetronic Acids

The highly acidic tetronic acid **15** and 3-methyltetronic acid **25** (furan numbering) are efficiently allylated under Pd(0) catalysis (88T7205,

88TL581). The reactions of **15** are, in general, difficult to control at the monoallylation step, even when working with one equivalent of allylating agent as in the formation of **19** (see Scheme 6). Even with severely hindered allylating agents such as 2-cyclohexenyl acetate **22**, the monoreaction product **23** is accompanied by significant amounts of diallylated **24**, although in this case, as in the conversion of **15** into **19**, more than one equivalent of allylating agent was required to ensure total conversion of **15**. Diallylations are efficiently achieved, as the conversion of **15** into **17** and into **20** with



a.- Pd(acac)<sub>2</sub> (5%), PPh<sub>3</sub> (20%), DBU (1 eq), THF, 60-5 ° C.  
b.- H<sub>2</sub> / Pd-C / EtOH

88TL581, 88T7205

SCHEME 6

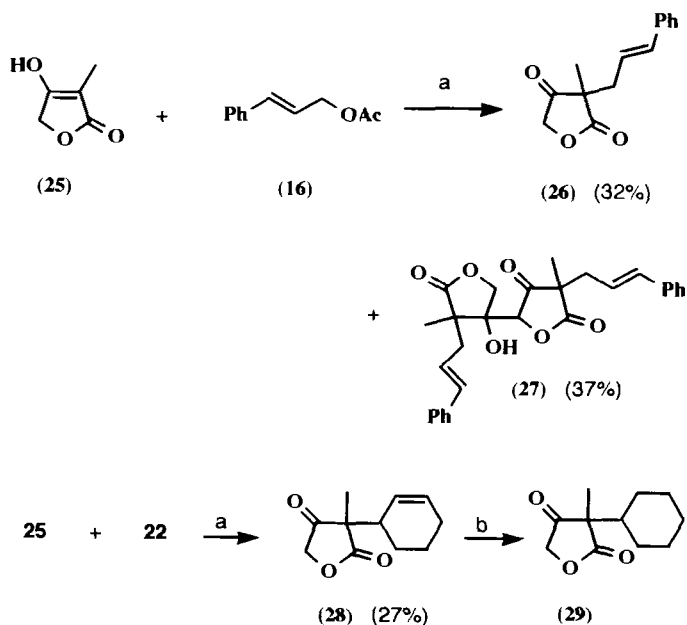
two or more equivalents of allylating agent. The usual (alkyl halide, base) allylation at oxygen has never been observed under Pd(0) catalysis.

Of course, the method is good for the allylation of the already monosubstituted methyltetronic acid **25**, which is converted into **26** and **28**, as shown in Scheme 7. And since hydrogenations of the allyl chain are easily performed, the two-step combination of Pd(0)-catalyzed allylation plus hydrogenation is a convenient alkylation method, as in the formation of **21** and **29**.

The monoallylation of tetronic acid can be achieved by using it in large excess with respect to the allyl acetate (**30**). Node and co-workers used this method to prepare **31** as a step in the synthesis of the natural product **32** (94T8337), as shown in Scheme 8.

## 2. Ascorbic Acid (Vitamin C)

Allylations at oxygen are the rule with alkyl halide–base systems. However, ascorbic acid **33**, which is a tetronic acid derivative, has been allylated

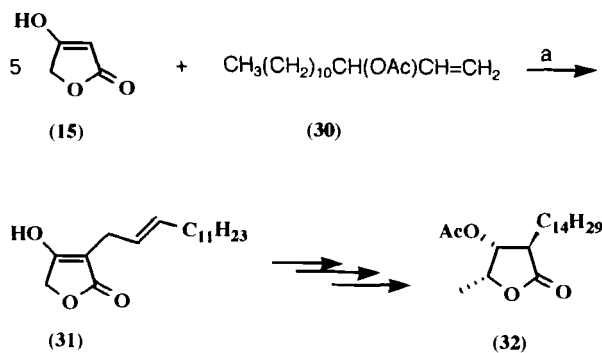


a.- Pd(acac)<sub>2</sub> (5%), PPh<sub>3</sub> (20%), DBU (1 eq), THF, 60-5 °C.

b.- H<sub>2</sub> / Pd-C / EtOH

88TL581, 88T7205

SCHEME 7

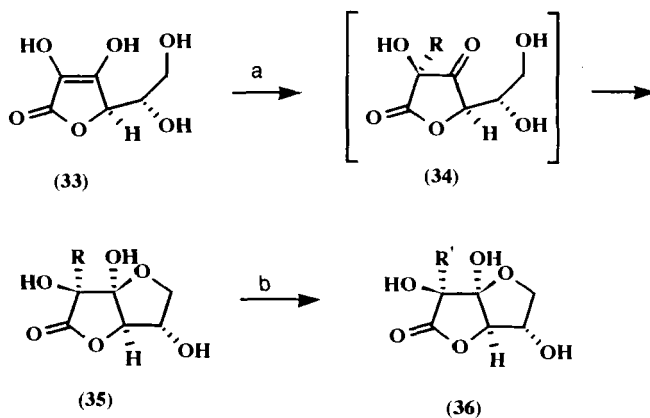


a. - Pd(acac)<sub>2</sub> (5%), PPh<sub>3</sub> (20%), DBU (1 eq), THF, 60°C

94T8337

SCHEME 8

at C-2 (ascorbic acid numbering throughout) under palladium(0) catalysis (Scheme 9) with a broad choice of allylating agents featuring primary and secondary allylic substrates (Table I). Radicals such as cinnamyl (**35a**), 2-butenyl (**35b**), 2-octenyl (**35c**), allyl (**35d**), 2-methylallyl (**35e**), 3-methyl-2-



a. - See Table I. b. - H<sub>2</sub> / Pd-C / EtOH

90JOC4925

R' = -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Ph (**36a**)

-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> (**36b**)

-C<sub>6</sub>H<sub>11</sub> (**36h**)

SCHEME 9

TABLE I  
 ALLYLATIONS OF L-ASCORBIC ACID (**33**)<sup>a</sup>

R-X	Pd source/L <sup>b</sup>	t (h)	<b>35</b> (%)
PhCH=CHCH <sub>2</sub> OAc	Pd(dba) <sub>2</sub> /DPPE	5	<b>35a</b> (28)
PhCH=CHCH <sub>2</sub> OAc	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	3	<b>35a</b> (23)
PhCH=CHCH <sub>2</sub> OCO <sub>2</sub> Et	Pd(dba) <sub>2</sub> /DPPE	5	—
PhCH=CHCH <sub>2</sub> OCO <sub>2</sub> Et	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	3.5	<b>35a</b> (41)
MeCH=CHCH <sub>2</sub> OCO <sub>2</sub> Et	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	4.5	<b>35b</b> (28)
CH <sub>2</sub> =CHCH(Me)OAc	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	2	—
CH <sub>2</sub> =CHCH(Me)OCO <sub>2</sub> Et	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	4	<b>35b</b> (57)
Me(CH <sub>2</sub> ) <sub>4</sub> (CH=CH <sub>2</sub> )OAc	Pd(dba) <sub>2</sub> /DPPE	5	<b>35c</b> <sup>c</sup> (23)
CH <sub>2</sub> =CHCH <sub>2</sub> OCO <sub>2</sub> Et	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	4	<b>35d</b> (70)
CH <sub>2</sub> =C(Me)CH <sub>2</sub> OCO <sub>2</sub> Et	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	2	<b>35e</b> (48)
Me <sub>2</sub> C=CHCH <sub>2</sub> OAc	Pd(dba) <sub>2</sub> /DPPE	8	—
Me <sub>2</sub> C=CHCH <sub>2</sub> OCO <sub>2</sub> Et	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	4	<b>35f</b> (38)
MeCH=CHCH(Me)OAc	Pd(dba) <sub>2</sub> /DPPE	22	<b>35g</b> <sup>d</sup> (5)
MeCH=CHCH(Me)OCO <sub>2</sub> Et	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	5	<b>35g</b> <sup>d</sup> (55)
2-Cyclohexenyl-OAc	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	4	—
2-Cyclohexenyl-OCO <sub>2</sub> Et	Pd(dba) <sub>2</sub> /DPPE	20	—
2-Cyclohexenyl-OCO <sub>2</sub> Et	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	12	<b>35h</b> <sup>d</sup> (48)

<sup>a</sup> Refluxing in THF for the indicated time. One equivalent of DBU is added when allylic acetates are used. <sup>b</sup> Pd (5%), PPh<sub>3</sub> (20%), or DPPE (10%). DPPE is 1,2-bis(diphenylphosphino)ethane. <sup>c</sup> Radical R in **35c**: Me(CH<sub>2</sub>)<sub>4</sub>CH=CHCH<sub>2</sub>—. <sup>d</sup> Diastereomeric mixture.

butenyl (**35f**), 3-penten-2-yl (**35g**), and 2-cyclohexenyl (**35h**) are introduced (90JOC4925). Two combinations of palladium sources and stabilizing phosphines were studied. For unknown reasons, the system Pd(acac)<sub>2</sub>/PPh<sub>3</sub> is better than the system Pd(dba)<sub>2</sub>/DPPE. This latter precatalytic system does not work well with mixed carbonates. The primary allylation products (**34**) were not isolated since they cyclized spontaneously to 2-allyl-3-oxo-L-gulonolactone 3,6-hemiketals (**35**). The allylation takes place through attack at the less hindered face of vitamin C. Compounds **35a,b,h** were hydrogenated to the fully saturated hemiketals **36a,b,h** (90JOC4925).

## B. RINGS CONTAINING OXYGEN AND NITROGEN

### 1. 3-Hydroxyisoxazoles

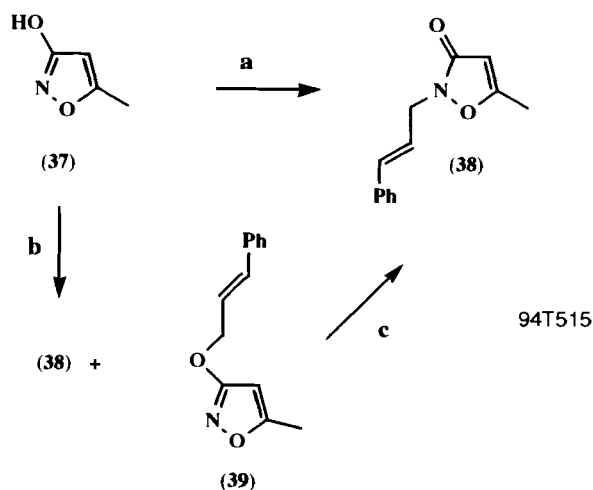
The cinnamyl system has frequently been adopted as the allylic system for regioselectivity studies since these derivatives are very reactive, they give solid, high-molecular-weight compounds, and moreover, they usually present a very regioselective reactivity, the attack by the nucleophile taking

place at the primary methylene group. Thus, 3-hydroxy-5-methylisoxazole (37) reacts with cinnamyl ethyl carbonate under Pd(0)-catalysis to give the *N*-allylated compound 38, as shown in Scheme 10. But the reaction of 37 with cinnamyl bromide in basic medium is not regioselective, leading to a mixture of 38 and the ether 39. When 39 is treated with the allylation precatalyst, it isomerizes completely to 38 ( $N > O$ ), thus indicating that the Pd(0)-catalyzed allylation is thermodynamically controlled (94T515).

## 2. Isoxazol-5-ones

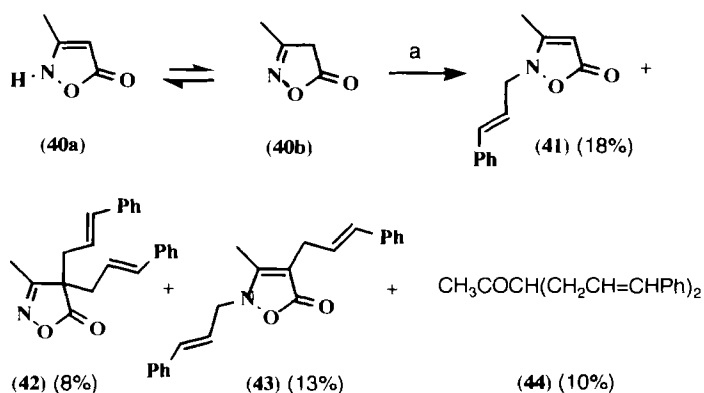
Isoxazol-5-ones, such as 40, present the tautomeric preferences as indicated in Scheme 11 (NH and CH tautomers predominating). Compound 40 reacts with cinnamyl ethyl carbonate under Pd(0)-catalysis to afford a mixture of *N*- and *C*-allylation products 41–44. Under forcing conditions, 43 is converted into 44 ( $C > N$ ), probably through intermediate 42. Therefore, the Pd(0)-catalyzed allylation can be driven under thermodynamic control, although products arising from ring cleavage appear (94T515).

The bicyclic isoxazol-5-ones 45 and 47 (Scheme 12) were regioselectively allylated at the nitrogen atom to afford compounds 46 and 48 with three different allylic systems featuring primary and secondary electrophilic cen-



- a.-  $\text{PhCH=CHCH}_2\text{OCO}_2\text{Et}$ ,  $\text{Pd(PPh}_3)_4$  (10%), refl. THF  
b.-  $\text{PhCH=CHCH}_2\text{Br}$ ,  $\text{K}_2\text{CO}_3$ , refl. acetone  
c.-  $\text{Pd(PPh}_3)_4$ , refl. THF

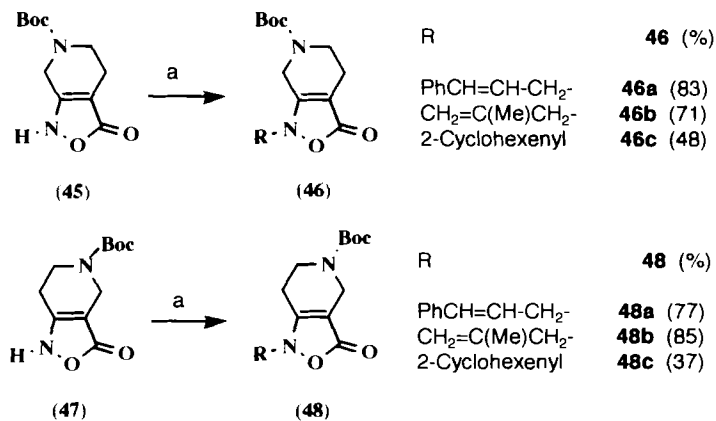
SCHEME 10



a -  $\text{PhCH}=\text{CHCH}_2\text{OCO}_2\text{Et}$ ,  $\text{Pd}(\text{PPh}_3)_4$  (5%), refl. THF  
 b -  $\text{Pd}(\text{PPh}_3)_4$  (10%),  $80 \rightarrow 140^\circ\text{C}$ , 100 h

94T515

SCHEME 11



a -  $\text{ROCO}_2\text{Et}$ ,  $\text{Pd}(\text{PPh}_3)_4$  (5-10%), refl. THF

94T515

SCHEME 12



ters. No allylation at carbon was observed as for isoxazolone **40**, since it would lead to the formation of sterically hindered quaternary centers (94T515).

### C. RINGS CONTAINING NITROGEN AND SULFUR

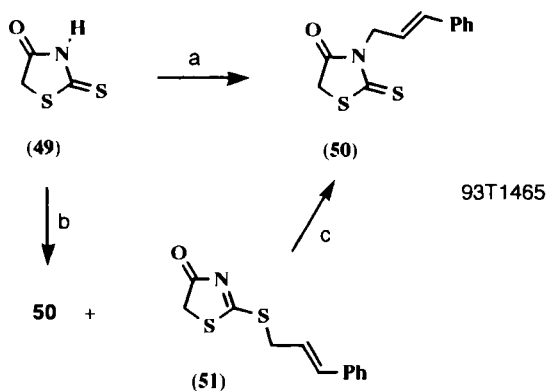
#### 1. *Thiazol-4-one-2-thione* (*Rhodanine*)

Direct allylation of rhodanine **49** (Scheme 13) under Pd(0)-catalysis with cinnamyl ethyl carbonate affords the *N*-allylated compound **50**. However, allylation with cinnamyl bromide and a base is not regioselective, producing a mixture of **50** and sulfide **51**. Sulfide **51** isomerizes to **50** under palladium catalysis ( $N > S$ ), thus indicating that Pd(0)-catalyzed allylation of **49** is thermodynamically controlled (93T1465).

### D. NITROGEN-CONTAINING RINGS

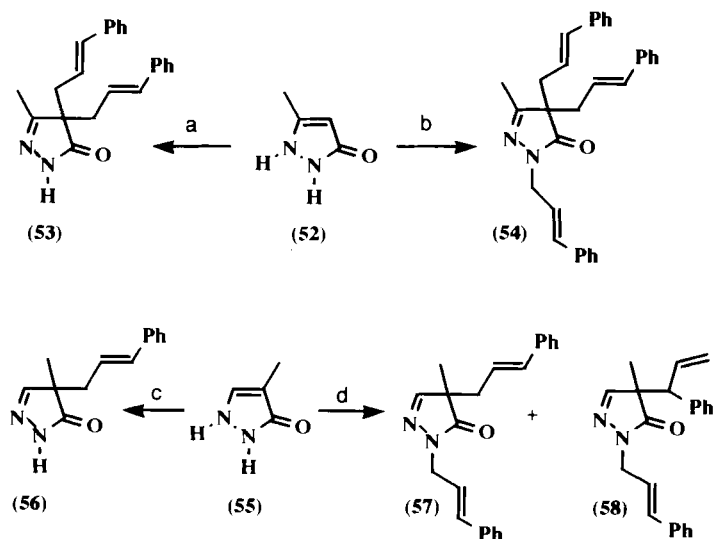
#### 1. *5-Pyrazolones*

3-Methyl-5-pyrazolone **52** (Scheme 14) is allylated at C-4 under Pd(0) catalysis, as exemplified by its transformation into **53**. Only when two allylic



- a. -  $\text{PhCH=CHCH}_2\text{OCO}_2\text{Et}$ ,  $\text{Pd}(\text{acac})_2$  (5%),  $\text{PPh}_3$  (20%), THF, r.t.  
 b. -  $\text{PhCH=CHCH}_2\text{Br}$ ,  $\text{K}_2\text{CO}_3$ , acetone, r.t.  
 c. -  $\text{Pd}(\text{PPh}_3)_4$  (5%), dioxane, refl., 60 h

SCHEME 13



- a. -  $\text{PhCH=CHCH}_2\text{OCO}_2\text{Me}$  (1.0 eq),  $\text{Pd(PPh}_3)_4$  (5%), refl. THF  
 b. -  $\text{PhCH=CHCH}_2\text{OCO}_2\text{Et}$  (3.5 eq),  $\text{Pd(PPh}_3)_4$  (5%), refl. THF  
 c. -  $\text{PhCH=CHCH}_2\text{OCO}_2\text{Et}$  (1.0 eq),  $\text{Pd(PPh}_3)_4$  (6%), refl. THF  
 d. -  $\text{PhCH=CHCH}_2\text{OCO}_2\text{Et}$  (2.4 eq),  $\text{Pd(PPh}_3)_4$  (8%), refl. THF

94T515

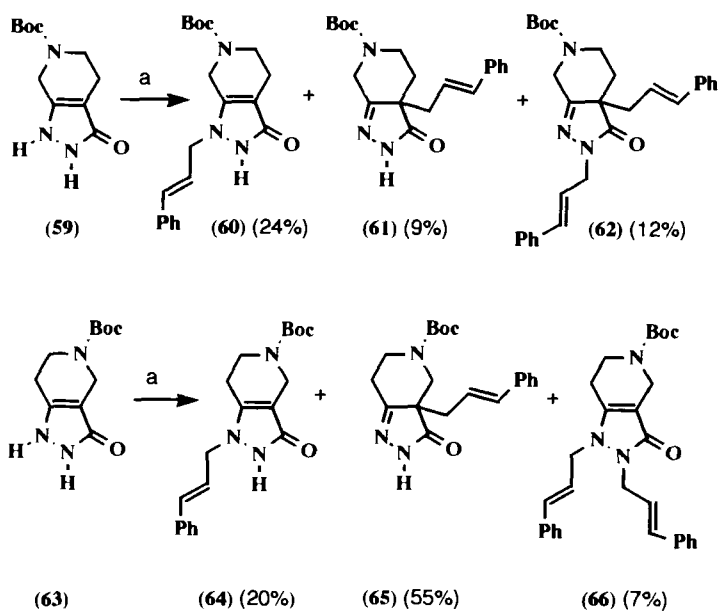
SCHEME 14

radicals have been introduced at C-4, does further allylation take place at N-1 to afford **54** (94T515). Similar behavior has been observed for the 4-methyl-5-pyrazolone isomer **55** (94T515).

Bicyclic 5-pyrazolones **59** and **63** (Scheme 15) also tend to be allylated at C-4 (pyrazolone numbering). However, as in the case of isoxazol-5-ones, steric hindrance militates against allylation at C-4 and allylation at N-2 occurs to a significant extent (94T515).

## 2. Imidazoles

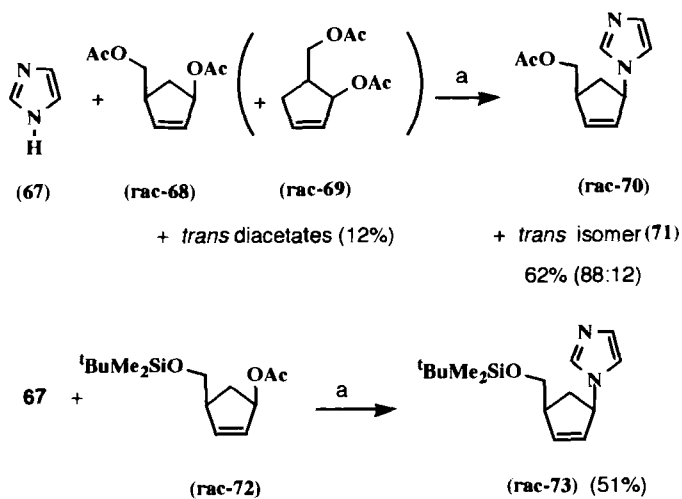
Lindell and co-workers reported [91JCS(P1)2603] that imidazole **67** reacts with a mixture of racemic acetates **68** and **69** containing 12% of *trans* isomers to afford isomers *cis*-**70** and *trans*-**71** in the same ratio as that obtaining in the *cis-trans* mixture of starting materials (Scheme 16). It should be pointed out that both **68** and **69** produce the same intermediate



a -  $\text{PhCH=CHCH}_2\text{OCO}_2\text{Et}$ ,  $\text{Pd(PPh}_3)_4$  (5-7%), refl. THF

94T515

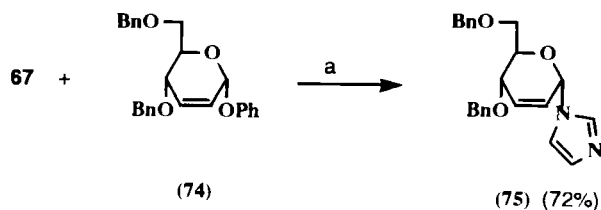
SCHEME 15



a -  $\text{Et}_3\text{N}$  (1.5 eq), cat.  $\text{Pd(PPh}_3)_4$ , refl. THF

91JCS(P1)2603

SCHEME 16



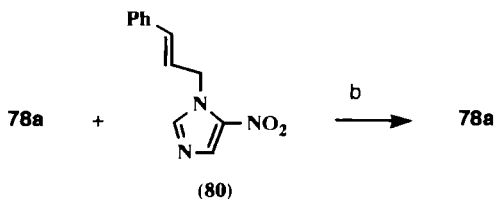
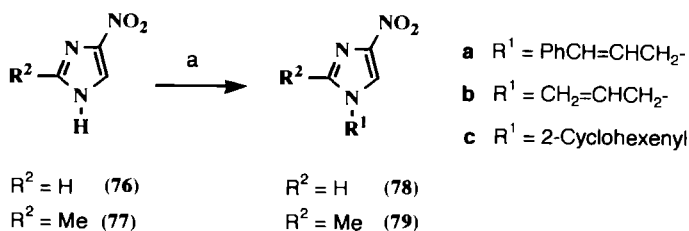
a.- Cat.  $\text{Pd}_2(\text{dba})_3$  / dppb, THF, 60-70°

92T2481

SCHEME 17

$\eta^3$ -allylpalladium cation which gives rise, regioselectively, to the same final product **70** generated from attack at the less hindered terminal of the allylic system. A similar result is exemplified by the reaction of **67** with *rac*-**72** to afford *rac*-**73** [91JCS(P1)2603].

When imidazole **67** is allylated with glycoside **74** (Scheme 17), product **75** is the only isolated compound, as reported by Sinou and co-workers (92TL2481). Again, the nonsymmetrical palladium intermediate is attacked at the less hindered point, but in this case, this point is, at the same time,



a.-  $\text{R}^1\text{OCO}_2\text{Me}$  (or Et), cat.  $\text{Pd}(\text{PPh}_3)_4$ , refl. THF for **77**;  
 DMSO at 70-80 °C for **76**

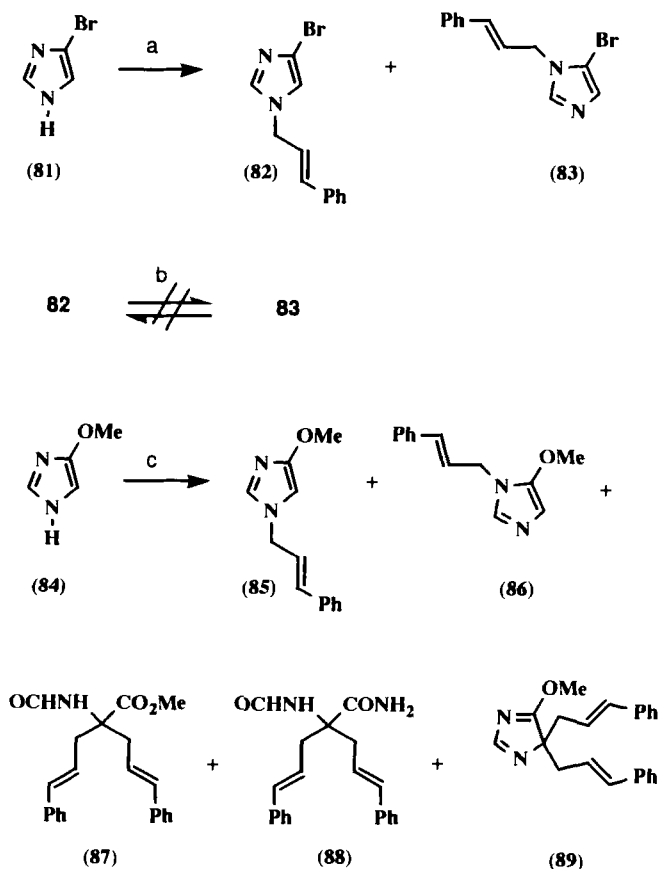
b.- Cat.  $\text{Pd}(\text{PPh}_3)_4$ , refl. THF

95JHC1325

SCHEME 18

proximal to the oxygen atom of the pyrane ring, which has an important directing effect.

4(5)-Nitroimidazoles **76** and **77** present a problem of regioselectivity between two atoms of the same chemical nature, i.e., two nitrogen atoms. The differences in reactivity are dictated by the nitro group present at C-4. Palladium(0)-catalyzed allylations of both **76** and **77** (Scheme 18) occur in such a way that only the 4-nitro derivatives **78** and **79** are produced with



a.- Several different Pd(0)-catalyzed allylations.

b.- Cat.  $\text{Pd}(\text{PPh}_3)_4$ , dioxane,  $140^\circ\text{C}$ .

c.-  $\text{PhCH}=\text{CHCH}_2\text{OCO}_2\text{Et}$ ,  $\text{Pd}(\text{PPh}_3)_4$ , refl. THF

95JHC1325

various allylating agents (95JHC1325). A mixture of isomers **78a** and **80** (5-nitro derivative) was obtained by reaction of **76** with cinnamyl bromide and base. When the mixture was treated under Pd(0) catalysis, isomerization of the 5-nitro derivative **80** to **78a** occurred, thus indicating that the Pd(0)-catalyzed allylation is thermodynamically controlled.

4(5)-Bromoimidazole **81** gave mixtures of the 4-bromo (**82**) and 5-bromo (**83**) isomers under Pd(0)-catalyzed allylation (Scheme 19). Isomerization was not observed, even under forcing conditions, thus indicating that the allylation reaction was kinetically controlled (95JHC1325). Important differences are therefore observed with different substituents on the imidazole ring: the nitro group renders the reaction reversible, but the bromine atom does not. This difference in behavior is attributable to the higher stabilization of the conjugate base of **76** (and of **77**) with respect to the conjugate base of **81**.

4(5)-Methoxyimidazole **84** was also allylated under Pd(0) catalysis. However, this reaction was not useful and gave a complicated array of products **85–89** arising from attacks at N-1, N-3, and C-5. Probably the experimental conditions were too severe for a very reactive imidazole such as **84** (95JHC1325).

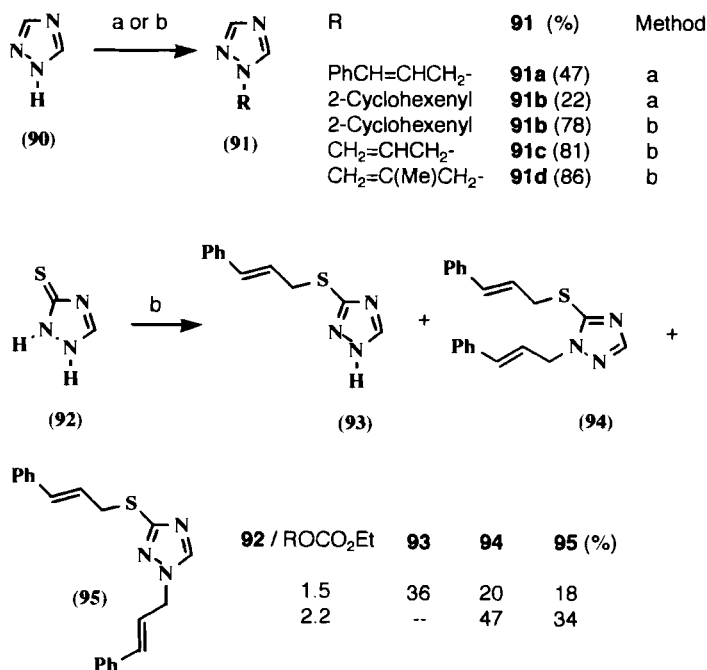
### 3. *Triazoles*

1,2,4-Triazole **90** (Scheme 20) is efficiently allylated at N-1 under Pd(0) catalysis, affording 1-allyltriazoles **91**. No N-4 allylation products were detected (93T1465). Under similar conditions, 1,2,4-triazolethione **92** is allylated at the sulfur atom under kinetic control to give sulfide **93**. If excess allylating agent is introduced, the second allylation takes place at N-1 or at N-2 to afford compounds **94** and **95** (93T1465).

## E. FIVE-MEMBERED HETEROCYCLIC RINGS FUSED TO A BENZENE RING

### 1. *Indole*

In one of the first papers on the subject, Billups *et al.* (80SC147) reported that the Pd(0)-catalyzed allylation of indole **96** with allyl acetate gave *N*-allyl- (**97**) and 3-allylindole (**98**) plus the diallylation product **99** (Scheme 21). They also showed that the *N*-allyl isomer **97** rearranged under Pd(0) catalysis to the C-3 isomer **98**, thus indicating that the formation of **98** was thermodynamically controlled (C > N). The work of Billups also includes the use of allyl alcohol instead of allyl acetate in the Tsuji-Trost reaction.



a. - ROCO<sub>2</sub>Et, cat. Pd(acac)<sub>2</sub>/PPh<sub>3</sub>, refl. THF

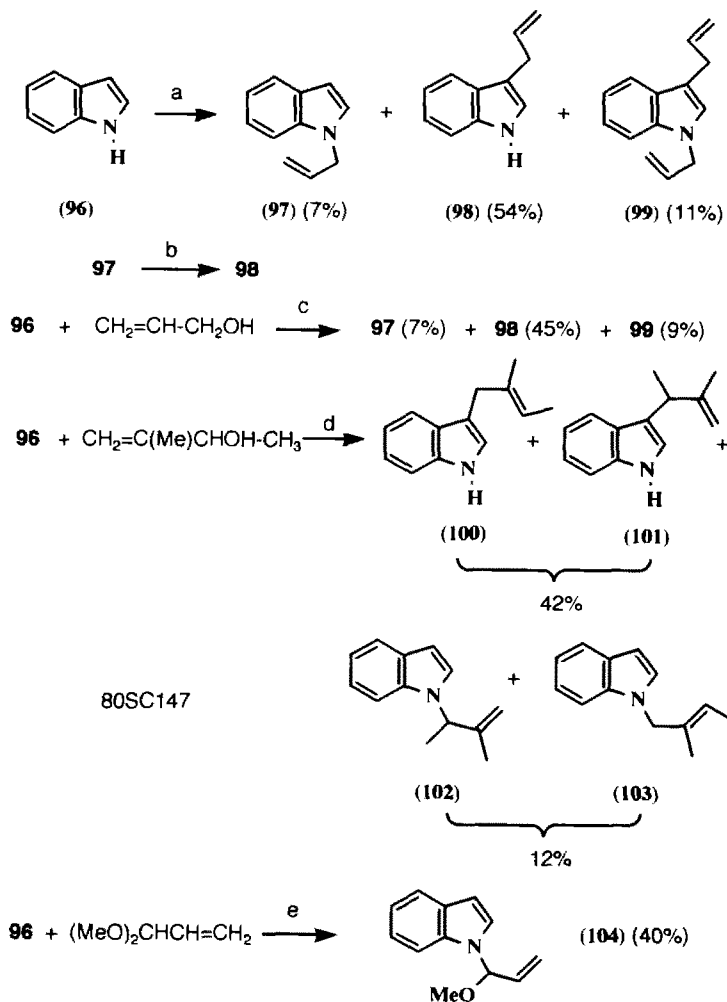
b. - ROCO<sub>2</sub>Et, cat. Pd(PPh<sub>3</sub>)<sub>4</sub>, refl. THF

93T1465

SCHEME 20

This is interesting because allylic alcohols are generally considered less active than their acetates. Another example included in the paper by Billups was the allylation of **96** with a secondary alcohol to afford a mixture **100–103** containing all possible isomers arising from lack of regioselectivity at both the nucleophile and the electrophile.

The Pd(0)-catalyzed allylation of **96** with acrolein dimethyl acetal gives exclusively compound **104**. The  $\eta^3$ -allylpalladium cationic complex (**4**, R = OMe) is attacked only at the center bearing the substituent MeO (80SC147), thus emphasizing the importance not only of steric effects in the electrophile but also of the electronic effects in the Tsuji–Trost reaction (92T1695). Indole **96** has been also allylated with epoxide **105** under Pd(0) catalysis by Trost and Molander (81JA5969). The intermediate cationic complex is attacked at the exocyclic position, **106** being formed, as shown in Scheme 22.



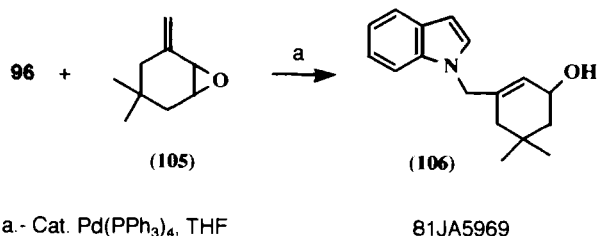
- a.-  $\text{CH}_2=\text{CHCH}_2\text{OAc}$ , cat.  $\text{Pd}(\text{acac})_2 / \text{PPh}_3$ , AcOH, 75 °C.  
 b.- Cat.  $\text{Pd}(\text{acac})_2 / \text{PPh}_3$ , AcOH, 75 °C.  
 c.- Cat.  $\text{Pd}(\text{acac})_2 / \text{PPh}_3$ , PhH, 85 °C.  
 d.- Cat.  $\text{Pd}(\text{acac})_2 / \text{PPh}_3$ , EtOH, 100 °C.  
 e.- As in c at 130 °C

SCHEME 21

## 2. Benzimidazoles

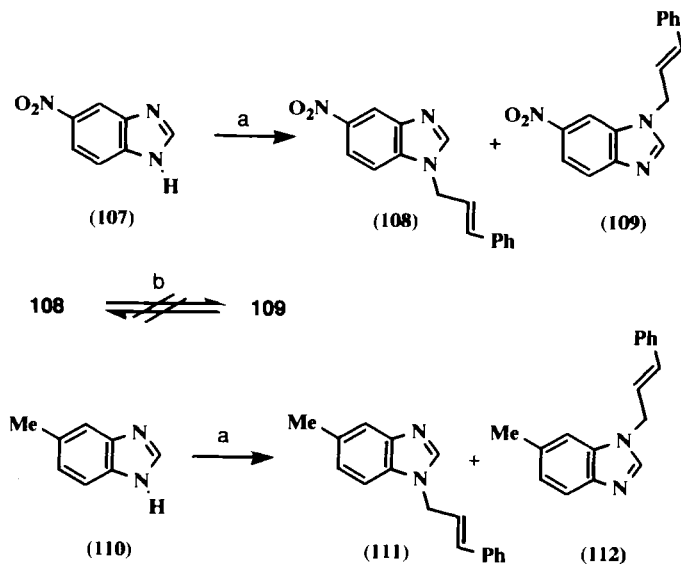
5(6)-Nitrobenzimidazole **107** and 5(6)-methylbenzimidazole **110** are efficiently allylated under Pd(0) catalysis (Scheme 23). Unfortunately, the





SCHEME 22

reactions are not regioselective, mixtures of allylnitroimidazoles **108** and **109** and of allylmethylimidazoles **111** and **112** being formed (95JHC1325). Attempts to interconvert isomers **108** and **109** under  $\text{Pd}(0)$  catalysis and forcing conditions failed. In contrast to its behavior in the imidazole series, the nitro group does not transmit its effect to the 5-membered ring when situated in the fused benzene ring.



a.- Several different  $\text{Pd}(0)$ -catalyzed allylations.  
 b.- Cat.  $\text{Pd}(\text{PPh}_3)_4$ , refl. dioxane.

95JHC1325

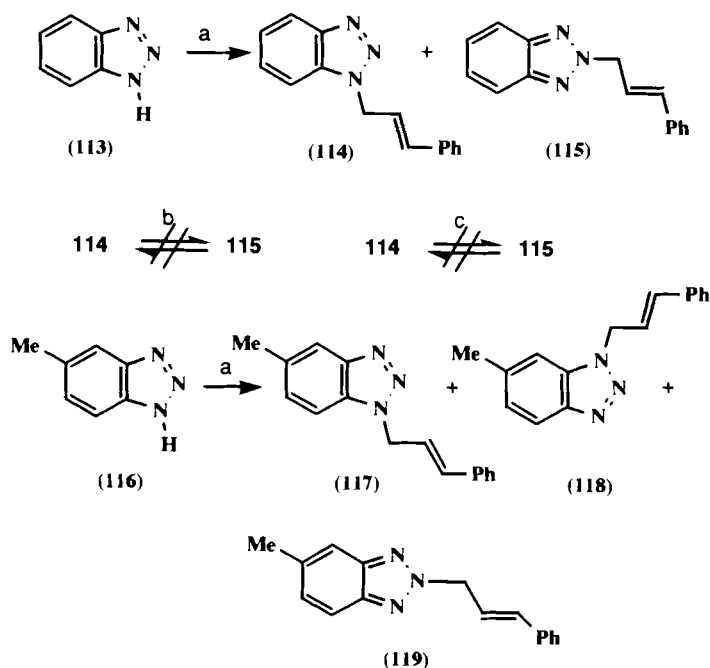
SCHEME 23

### 3. Benzotriazoles

Similar results to those reported for **107** and **110** were found for benzotriazoles **113** and **116**, which were efficiently, but not regioselectively, allylated. Many experimental conditions were tested (95JHC1325). However, mixtures of compounds **114** and **115** in one case and of **117–119** in the other were always formed (Scheme 24). Allylbenzotriazoles **114** and **115** do not equilibrate under Pd(0) catalysis.

### 4. Benzoxazolethione, Benzothiazolethione, and Benzimidazolethione

Benzoxazolethione **120** (Scheme 25) was first allylated by Sinou and co-workers to afford sulfide **121** (R = H) (92TL8099; 94T10321). When the



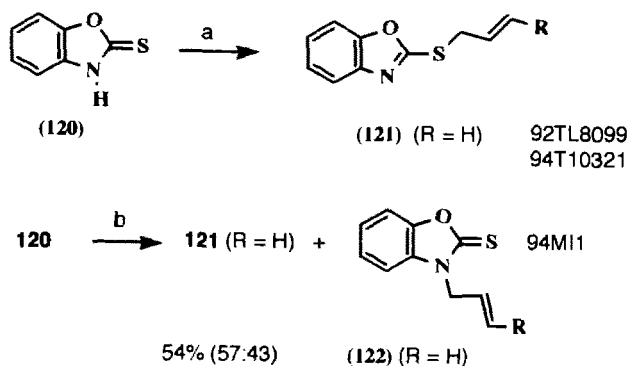
a. - Several different Pd(0)-catalyzed allylations.

b. - Cat.  $\text{Pd}(\text{PPh}_3)_4$ , refl. THF.

c. - Cat.  $\text{Pd}(\text{PPh}_3)_4$ , refl. dioxane.

95JHC1325

SCHEME 24



a.-  $\text{CH}_2=\text{CHCH}_2\text{OCO}_2\text{Me}$ , cat.  $\text{Pd}(\text{dba})_2$  /  $\text{dppb}$ , THF,  $50^\circ\text{C}$

b.-  $\text{CH}_2=\text{CHCH}_2\text{OAc}$ , KF, Cat  $\text{Pd}(\text{dba})_2$  /  $\text{dppb}$ , THF, r.t.

SCHEME 25

allylation of **120** is performed with allyl acetate using potassium fluoride as a base (94MI1), a mixture of sulfide **121** ( $\text{R} = \text{H}$ ) and *N*-allylbenzoxazolethione **122** ( $\text{R} = \text{H}$ ) is formed.

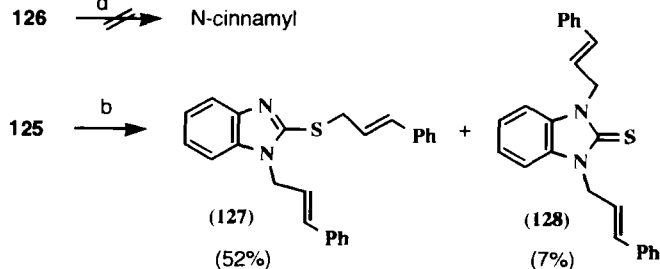
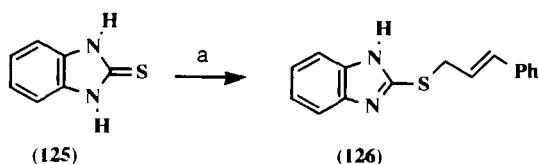
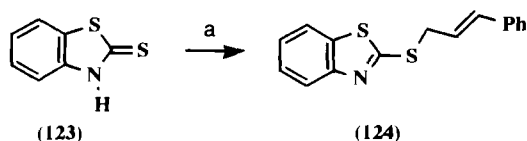
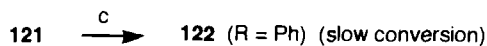
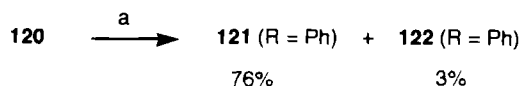
The Pd(0)-catalyzed allylations of **120**, benzothiazolethione **123**, and benzimidazolethione **125** (Scheme 26) have been studied by the current authors (93T1465). In all cases, the sulfides **121** ( $\text{R} = \text{Ph}$ ), **124**, and **126** were formed, either as major or as exclusive products. Attempts to isomerize sulfides into *N*-cinnamyl derivatives were made. Slow conversions were observed for sulfides **121** ( $\text{R} = \text{Ph}$ ) and **124** under forcing conditions, thus indicating that sulfides are the products of kinetic control and the *N*-cinnamyl derivatives are the products of the thermodynamic control ( $\text{N} > \text{S}$ ), which is not easily attainable. Of course, the reaction of **125** with two equivalents of allylating agent gives the *S,N*-dicinnamyl derivative **127**.

### III. Six-Membered Heterocyclic Rings

#### A. OXYGEN-CONTAINING RINGS

##### 1. 4-Hydroxy-6-methyl-2-pyrone (Triacetic Acid Lactone)

The reversibility of *O*-allylation and the stereochemistry of the Pd(0)-catalyzed allylations have been studied in triacetic acid lactone **129**, a natural polyketide. Thus, efficient and controlled *C*-allylations of **129** take place under Pd(0) catalysis to afford monoallylation products **130** (in toluene)



a.-  $\text{PhCH=CHCH}_2\text{OCO}_2\text{Et}$ , cat.  $\text{Pd}(\text{PPh}_3)_4$ , THF, r.t.

b.- As in a with 2 eq. of  $\text{PhCH=CHCH}_2\text{OCO}_2\text{Et}$ .

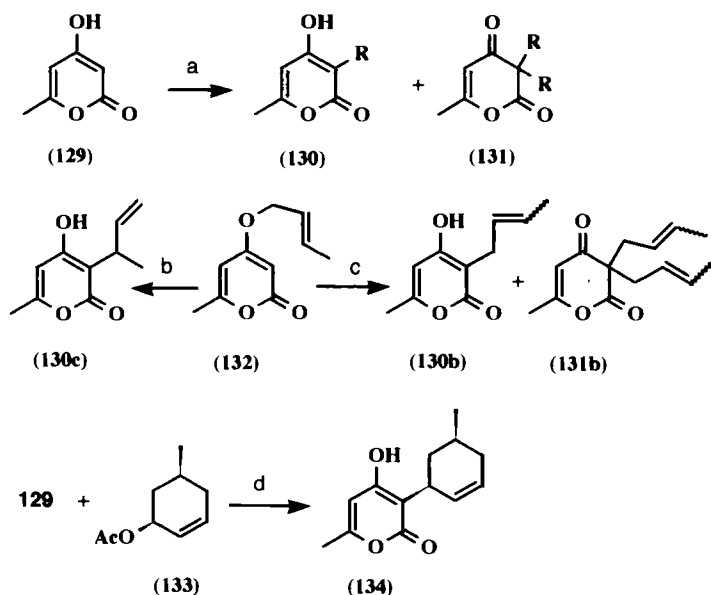
c.- Cat.  $\text{Pd}(\text{PPh}_3)_4$ , dioxane, 140 °C.

d.- Cat.  $\text{Pd}(\text{PPh}_3)_4$ , refl. THF.

93T1465

SCHEME 26

or diallylation products **131** (in THF) (see Scheme 27 and Table II) (88JOC5328, 88TL581). Enol ether **132**, prepared by Mitsunobu reaction of **129**, rearranges thermally to **130c** in a typical intramolecular Claisen



a. - See Table II.

b. - Refl. toluene.

c. - Cat.  $\text{Pd}(\text{acac})_2$  /  $\text{PPh}_3$ , toluene, 82 °C.

d. - Cat.  $\text{Pd}(\text{acac})_2$  /  $\text{PPh}_3$ , DBU (1 eq), toluene, 80 °C.

88TL581, 86JOC5328

SCHEME 27

TABLE II  
ALLYLATIONS OF TRIACETIC ACID LACTONE (129)<sup>a</sup>

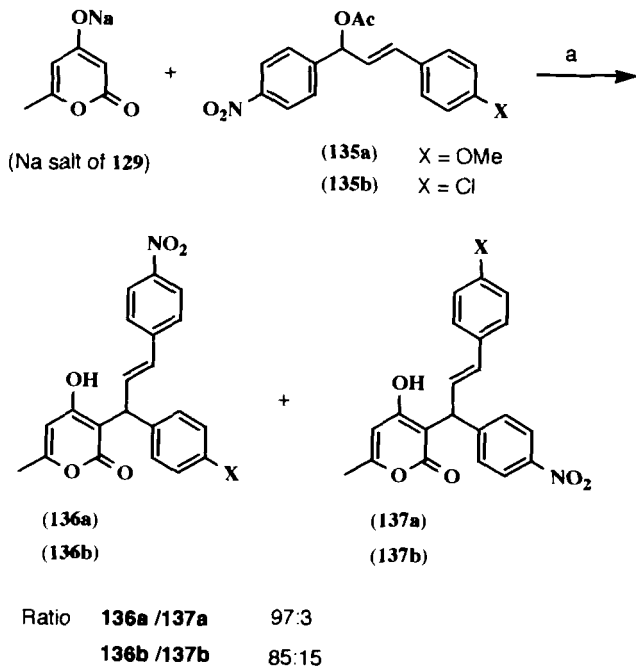
R-X (number of equivalents)	Solvent/T (°C)/t (h)	Base	130 (%)	131 (%)
( <i>E</i> )-PhCH=CHCH <sub>2</sub> OAc (1.0)	toluene/74/2.5	—	<b>130a</b> (83)	—
( <i>E</i> )-PhCH=CHCH <sub>2</sub> OAc (1.0)	toluene/70/2	DBU	<b>130a</b> (66)	—
( <i>E</i> )-PhCH=CHCH <sub>2</sub> OAc (1.0)	THF/r.t./25	—	<b>130a</b> (37)	<b>131a</b> (49)
( <i>E</i> )-PhCH=CHCH <sub>2</sub> OAc (2.5)	THF/40/69	—	—	<b>131a</b> (73)
( <i>E</i> )-MeCH=CHCH <sub>2</sub> OAc (1.0)	toluene/70/8	DBU	<b>130b</b> <sup>b</sup> (63) <b>130c</b> <sup>c</sup> (23)	—
( <i>E</i> )-MeCH=CHCH <sub>2</sub> OAc (2.5)	THF/40/71	—	—	<b>131b</b> (51)
CH <sub>2</sub> =CHCH(Me)OAc (1.0)	toluene/76/3	DBU	<b>130b</b> <sup>d</sup> (59) <b>130c</b> <sup>c</sup> (20)	—
( <i>E</i> )-MeCH=CHCH(Me)OAc (1.0)	toluene/76/2	DBU	<b>130d</b> (47)	—
2-Cyclohexenyl-OAc (1.0)	toluene/72/1	DBU	<b>130e</b> (58)	—

<sup>a</sup>  $\text{Pd}(\text{acac})_2/\text{PPh}_3$  as precatalytic system. <sup>b</sup> (1:4) *Z-E* Mixture. <sup>c</sup> R in **130c** CH<sub>2</sub>=CH-CH(Me). <sup>d</sup> Mixture of isomers.

rearrangement; however, when treated under Pd(0) catalysis, intermolecular O-to-C rearrangement took place through the  $\eta^3$ -allylic complex to afford **130b** and **131b**. Palladium(0)-catalyzed reaction of **129** with *cis*-**133** afforded *cis*-**134**, thus indicating retention of configuration (88JOC5328).

Farina has shown that the reaction of **129** with cinnamyl chloride in THF with Pd<sub>2</sub>(dba)<sub>3</sub> and tri-(2-furyl)phosphine as precatalytic system, results in incomplete formation of the C-allylated **130a**, the isomeric cinnamyl ether of **129** being also isolated (91JA9585).

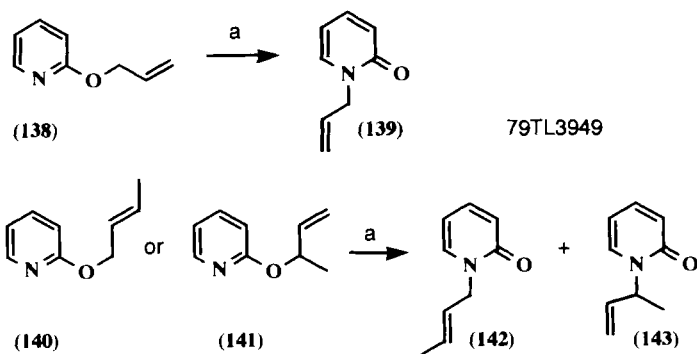
Pyrone **129** has been used to study the regiochemistry at the electrophile. The cationic  $\eta^3$ -allylpalladium intermediate arising from **135** is the same as the one arising from the allylic isomer of **135**. Moreover, the steric requirements at both ends of the allylic system are supposed to be the same and, therefore, any regioselection should originate in electronic factors. Thus, the Pd(0)-catalyzed allylations of **129** with acetates **135** (and allylic isomers) afford **136** as the major products (Scheme 28), which arise from attack of the nucleophile at the allylic terminal most remote from the most electron-withdrawing substituent (NO<sub>2</sub>) (89TL3109; 92T1695).



a. - Cat. Pd(dba)<sub>2</sub> / PPh<sub>3</sub>, THF, r.t.

89TL3109, 92T1695

SCHEME 28



a.- Cat.  $\text{Pt}(\text{PPh}_3)_4$ , THF or DMF, 65 °C

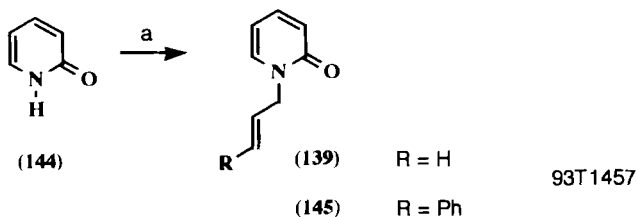
SCHEME 29

## B. NITROGEN-CONTAINING RINGS

### 1. 2-Pyridone and Pyridine-2-thione

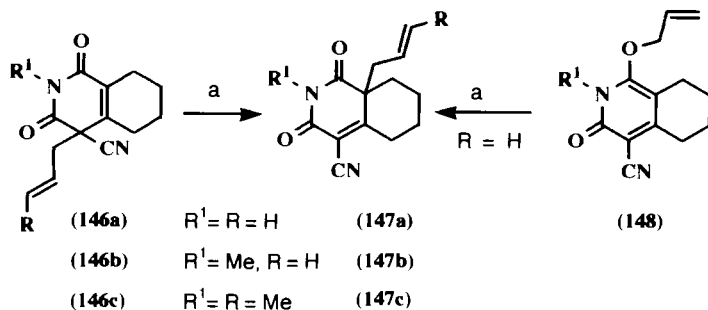
Perhaps the seminal work on the subject of this review is that of Balavoine and Guibé. They studied the  $\text{Pt}(0)$ -catalyzed (not  $\text{Pd}$ ) isomerization of 2-allyloxypyridine **138** (Scheme 29) into *N*-allyl-2-pyridone **139** ( $\text{N} > \text{O}$ ) (79TL3949). The intermolecular nature of the rearrangement, through a common  $\eta^3$ -allylplatinum intermediate, is indicated by the transformations of both ethers **140** and **141** into the same mixture of *N*-allylated isomers **142** and **143**.

Direct  $\text{Pd}(0)$ -catalyzed *N*-allylation of 2-pyridone **144** to compounds **139** and **145** has been also reported (93T1457), as shown in Scheme 30.



a.-  $\text{PhCH=CHCH}_2\text{OCO}_2\text{Et}$  or  $\text{CH}_2=\text{CHCH}_2\text{OCO}_2\text{Et}$ ,  
cat.  $\text{Pd}(\text{acac})_2 / \text{PPh}_3$ , THF, r.t.

SCHEME 30

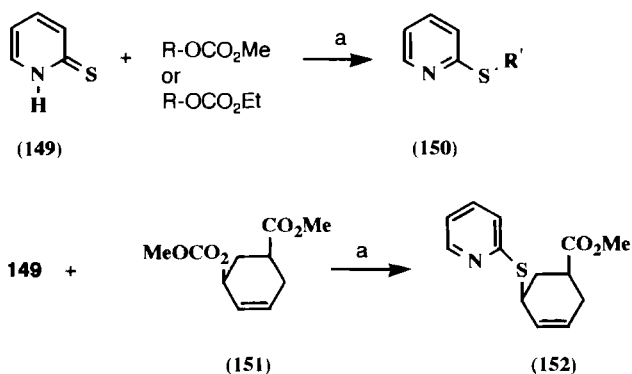
a. - Cat.  $\text{Pd}(\text{PPh}_3)_4$ , THF or PhH, r.t.

92TL1377

SCHEME 31

The interesting Pd(0)-catalyzed rearrangements of **146** and **148** to **147** (Scheme 31) have been reported by van der Baan *et al.* (92TL1377). These results point out that C-allylation products are thermodynamically more stable than O-allylation products ( $\text{C} > \text{O}$ ).

Sinou's group reported that the Pd(0)-catalyzed allylation of pyridine-2-thione **149** occurs at the sulfur atom to afford sulfides **150** (Scheme 32; Table III) (92TL8099; 94T10321). The reaction of **149** with the *cis*-cyclohexenyl carbonate **151** affords **152**, with overall retention of configuration.

a. - Cat.  $\text{Pd}_2(\text{dba})_3$  / dppb, THF, 50 °C. See Table III.

92TL8099, 94T10321

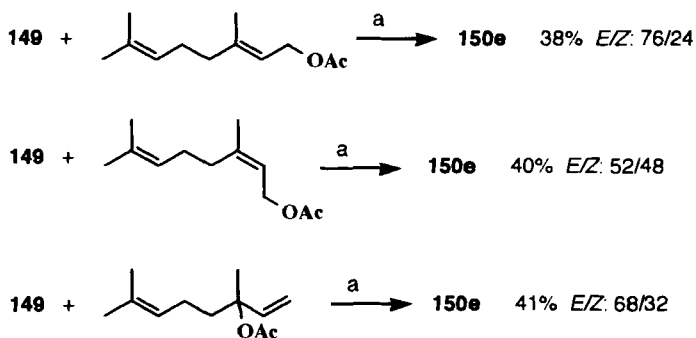
SCHEME 32



TABLE III  
ALLYLATIONS OF 2-THIOPYRIDONE (**149**)

R	R'	<b>150</b> (%)
CH <sub>2</sub> =CHCH <sub>2</sub> —	CH <sub>2</sub> =CHCH <sub>2</sub> —	<b>150a</b> (86)
PhCH=CHCH <sub>2</sub> —	PhCH=CHCH <sub>2</sub> —	<b>150b</b> (74)
2-Cyclohexenyl	2-Cyclohexenyl	<b>150c</b> (89)
CH <sub>2</sub> =CHC(Me) <sub>2</sub> —	Me <sub>2</sub> C=CHCH <sub>2</sub> —	<b>150d</b> (51)
( <i>E</i> )-Me <sub>2</sub> C=CHCH <sub>2</sub> CH <sub>2</sub> C(Me)=CHCH <sub>2</sub> —	( <i>E</i> )-Me <sub>2</sub> C=CHCH <sub>2</sub> CH <sub>2</sub> C(Me)=CHCH <sub>2</sub> —	<b>150e</b> (43) <i>E/Z</i> : 76/24
MeCH <sub>2</sub> CH <sub>2</sub> CH=CHCH <sub>2</sub> —	MeCH <sub>2</sub> CH <sub>2</sub> CH=CHCH <sub>2</sub> —	<b>150f</b> <i>E/Z</i> : 85/15
	MeCH <sub>2</sub> CH <sub>2</sub> CH(CH=CH <sub>2</sub> )—	<b>150g</b> <b>150f</b> + <b>150g</b> (98%); <i>g</i> : 95/5
MeCH <sub>2</sub> CH <sub>2</sub> CH(CH=CH <sub>2</sub> )—	MeCH <sub>2</sub> CH <sub>2</sub> CH=CHCH <sub>2</sub> —	<b>150f</b> <i>E/Z</i> : 85/15
	MeCH <sub>2</sub> CH <sub>2</sub> CH(CH=CH <sub>2</sub> )—	<b>150g</b> <b>150f</b> + <b>150g</b> (96%); <i>g</i> : 98/2
( <i>Z</i> )-BnO—CH <sub>2</sub> CH=CHCH <sub>2</sub> —	BnO—CH <sub>2</sub> CH=CHCH <sub>2</sub> —	<b>150h</b> (92) <i>E/Z</i> : 90/10

Potassium fluoride can also be used as a base in the Pd(0)-catalyzed reactions of **149** with allylic acetates, as shown in Scheme 33 (94MI1). Sinou and co-workers reported that the acetates of the isomeric geraniol, nerol, and linalool gave similar mixtures of final sulfides **150e** (94MI1).



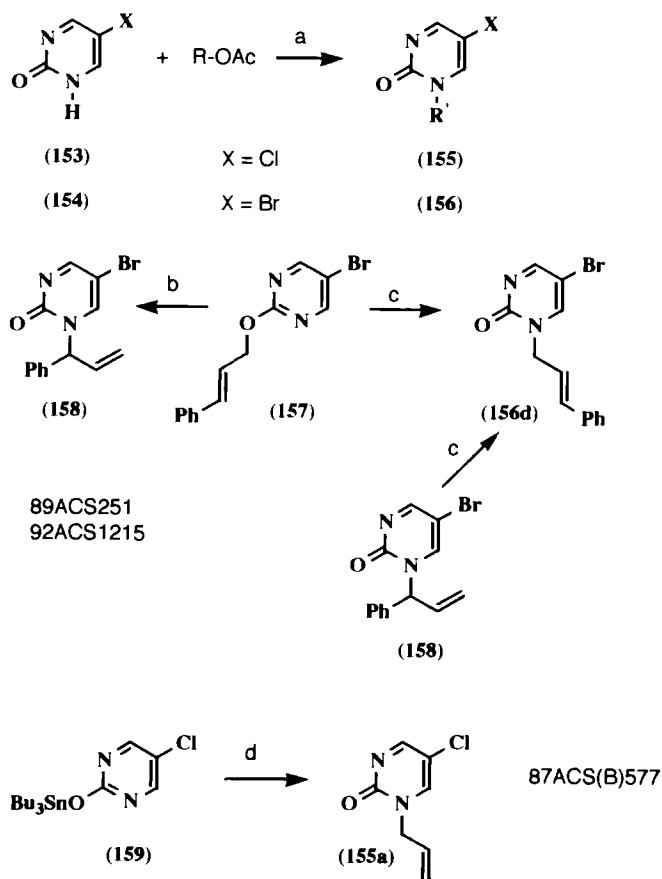
a.- Cat. Pd<sub>2</sub>(dba)<sub>3</sub> / dppb, KF, THF, r.t.

94MI1

SCHEME 33

2. *Pyrimidin-2-one and Pyrimidine-2-thione*

Benneche and Undheim have published extensive studies on the allylation of pyrimidin-2-ones. A summary of their results is given below.



a. -  $\text{NEt}_3$ , cat.  $\text{Pd}(\text{OAc})_2 / (\text{O}^i\text{Pr})_3\text{P}$ ,  $\text{Cl}_2\text{CH}_2$ , r.t.

b. - Cat.  $\text{PdCl}_2(\text{PhCN})_2$ , refl. THF

c. - Cat.  $\text{Pd}(\text{OAc})_2 / (\text{O}^i\text{Pr})_3\text{P}$ , refl. THF

d. -  $\text{CH}_2=\text{CHCH}_2\text{OAc}$ , cat.  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{PhH}$ , r.t.

SCHEME 34

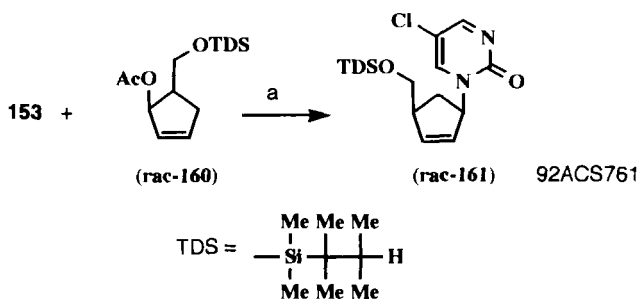
TABLE IV  
ALLYLATIONS OF PYRIMIDIN-2-ONES **153** AND **154**

X	R	R'	<b>155</b> or <b>156</b> (%)
Cl	CH <sub>2</sub> =CHCH <sub>2</sub> -	CH <sub>2</sub> =CHCH <sub>2</sub> -	<b>155a</b> (94)
Br	CH <sub>2</sub> =C(Me)CH <sub>2</sub> -	CH <sub>2</sub> =C(Me)CH <sub>2</sub> -	<b>156b</b> (73)
Br	MeCH=CHCH <sub>2</sub> -	MeCH(CH=CH <sub>2</sub> )-	<b>156c</b> (46)
Br	PhCH=CHCH <sub>2</sub> -	PhCH=CHCH <sub>2</sub> -	<b>156d</b> (50)
Cl	CH <sub>2</sub> =CHCH(C <sub>5</sub> H <sub>11</sub> )-	C <sub>5</sub> H <sub>11</sub> CH=CHCH <sub>2</sub> -	<b>155e</b> (57)
Br	CH <sub>2</sub> =CHCH(C <sub>5</sub> H <sub>11</sub> )-	C <sub>5</sub> H <sub>11</sub> CH=CHCH <sub>2</sub> -	<b>156e</b> (65)
Br	Me <sub>2</sub> C=CHCH <sub>2</sub> -	Me <sub>2</sub> C=CHCH <sub>2</sub> -	<b>156f</b> (46)
Cl	Me <sub>3</sub> SiCH=CHCH(C <sub>5</sub> H <sub>11</sub> )-	Me <sub>3</sub> SiCH=CHCH(C <sub>5</sub> H <sub>11</sub> )-	<b>155g</b> (17)

Compounds **153** and **154** (Scheme 34) give directly *N*-allylic derivatives **155** and **156** under Pd(0) catalysis (Table IV) (89ACS251; 92ACS1215).

The isomeric ether **157** and *N*-allylic derivative **158** rearrange to the same *N*-allylated product **156d** under Pd(0) catalysis through the usual cationic  $\eta^3$ -palladium complex; it should be mentioned that part of the added phosphite reduces Pd(II) to Pd(0). However, treatment of **157** under PdCl<sub>2</sub> catalysis gives **158** in which the branched chain appears at N-1. This is a different reaction, which consists of a Claisen [3,3]-rearrangement catalyzed specifically by palladium(II) chloride (89ACS251; 92ACS1215). Previous allylations by the same group were performed on the stannyl derivative **159** [87ACS(B)577].

The Pd(0)-catalyzed allylation of **153** (Scheme 35) with the racemic *cis*-cyclopentenyl acetate derivative **160** affords compound **161** with retention of configuration (92ACS761).



a. - Et<sub>3</sub>N, cat. Pd(OAc)<sub>2</sub> / (O<sup>i</sup>Pr)<sub>3</sub>P, Cl<sub>2</sub>CH<sub>2</sub>, r.t.

SCHEME 35

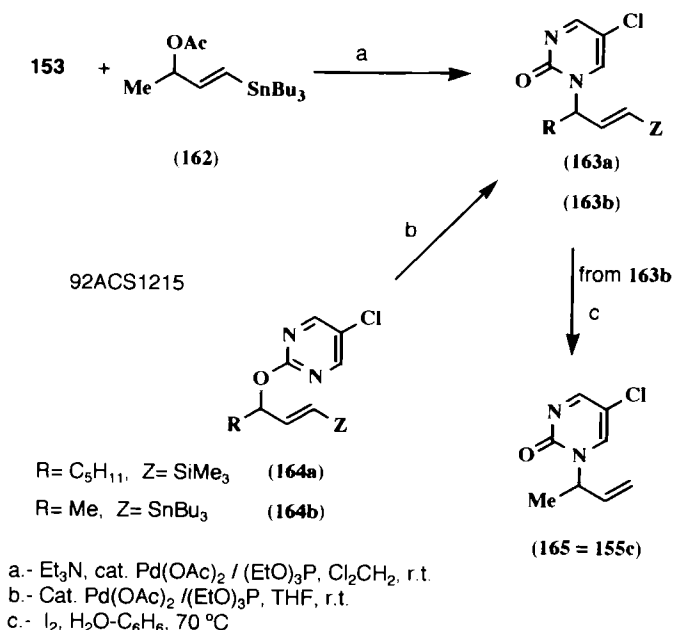
The reaction of **153** with the stannylated acetate **162** (Scheme 36) shows the directing effect of the  $\text{Bu}_3\text{Sn}$  group. Both direct allylation and rearrangement of **164** give **163**. Tin elimination from **163b** (step c) results in the incorporation of a branched 2-butenyl chain in **165** (92ACS1215).

Uracil-type compounds are insoluble in common organic solvents. Radicals  $\text{R}^4$  in **168** have been used to permit a more facile allylation or rearrangement to **167**, as shown in Scheme 37). Further transformation into the amide functional group permits preparation of **169**, and finally **170** (93ACS72).

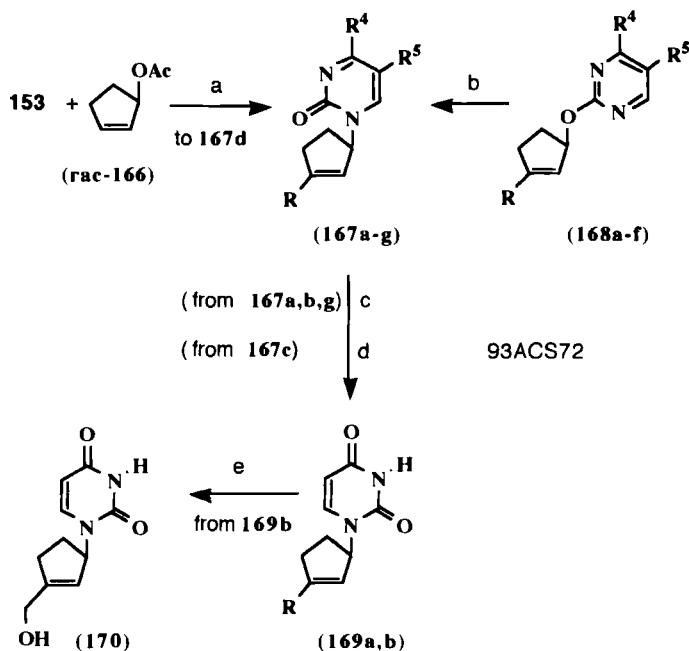
Other rearrangements (Scheme 38) are exemplified by the conversions of *rac*-**171** into *rac*-**172** (93ACS72) and of the mixed carbonates **173** into *N*-allylated compounds **155** and **156** (93ACS63).

Apart from the work done by Benneche and Undheim, Trost *et al.* have reported the Pd(0)-catalyzed reactions of the unsubstituted pyrimidin-2-one **174** (Scheme 39) with several vinyloxydes to afford products **175**–**178** (88JA621).

Pyridine-2-thione **179** reacts at the sulfur atom in Pd(0)-catalyzed allylation to afford sulfides **180** (Scheme 40), as reported by Sinou and co-workers (92TL8099; 94MI1, 94T10321).



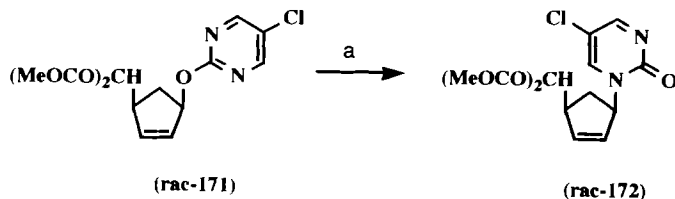
SCHEME 36



a.-  $\text{Cs}_2\text{CO}_3$  (1 eq), cat.  $\text{Pd}(\text{OAc})_2 / (\text{EtO})_3\text{P}$ , DMF. b.- Cat.  $\text{Pd}(\text{OAc})_2 / (\text{EtO})_3\text{P}$ , THF, r.t. c.-  $\text{NaOH}$ ,  $\text{H}_2\text{O}$ , r.t. d.-  $\text{FNBu}_4$ ,  $\text{CH}_3\text{CN}$ , r.t. e.-  $\text{HCl}$ ,  $\text{MeOH}$ ,  $60^\circ\text{C}$

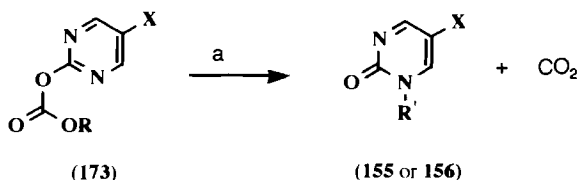
	R	R <sup>4</sup>	R <sup>5</sup>
<b>167a</b>	H	SMe	H
<b>167b</b>	$\text{CH}_2\text{OCH}_2\text{OMe}$	SMe	H
<b>167c</b>	H	$\text{OCH}_2\text{CH}_2\text{SiMe}_3$	H
<b>167d</b>	H	H	Cl
<b>167e</b>	Me	H	Cl
<b>167f</b>	$\text{CH}_2\text{OCH}_2\text{OMe}$	H	Cl
<b>167g</b>	H	Cl	H

SCHEME 37



a. - Cat.  $\text{Pd}(\text{OAc})_2 / (\text{EtO})_3\text{P}$ ,  $\text{CH}_3\text{CN}$ , r.t.

93ACS72



a. - Several different  $\text{Pd}(0)$  sources, THF, 20 or 80 °C

93ACS63

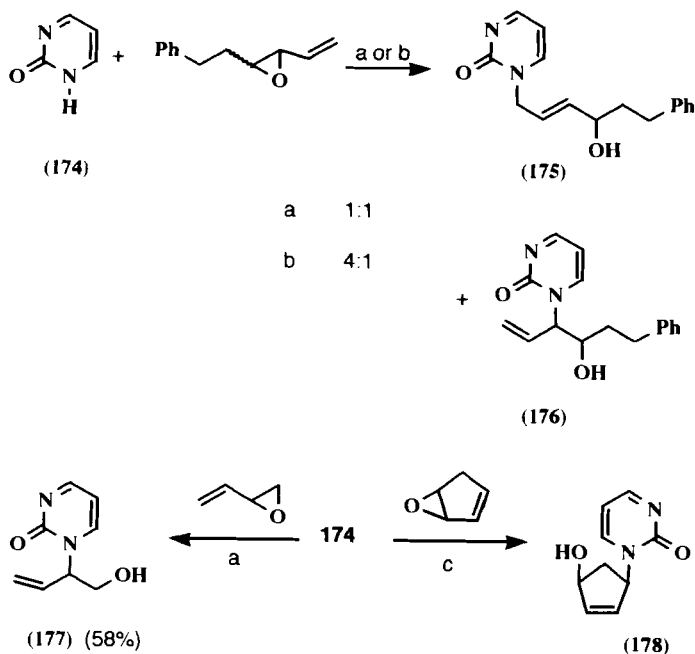
SCHEME 38

### 3. Uracils, Thiouracils, and Cytosine

In Section III.B.2, the difficulties inherent in the use of insoluble unmodified heterocycles were described, together with some methods of overcoming this difficulty reported by Benneche and Undheim. This problem is also encountered in the field of uracils. Thus, the same authors reported the  $\text{Pd}(0)$ -catalyzed allylation of the bis-(*O*-trimethylsilyl) derivative of thymine (**181**) which gives directly the mono- and the bis-*N*-allylated products **182** and **183** (Scheme 41). The same reaction with *rac*-**160** affords *rac*-**184**, with overall retention of configuration (92ACS761).

The same methodology has been used by Monneret and co-workers in the allylations of **181** to yield **185** and **186**, as well as in the allylations of thymine derivative **187** which afford **188** and **189** (94TL4351), as shown in Scheme 42). It can be concluded from both papers that the difference in reactivity between N-1 and N-3 is not high.

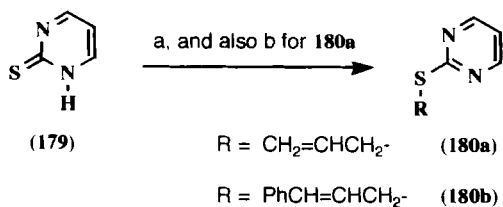
We have studied the direct allylation of uracil **190**, thymine **191**, and 6-methyluracil **192** (Scheme 43) under  $\text{Pd}(0)$  catalysis and forcing conditions (93T1457). The results are summarized in Table V. Uracil and thymine



- a.- Cat.  $\text{Pd}(\text{PPh}_3)_4$ , THF  
 b.- Cat.  $\text{Pd}(\text{P}(\text{O}^i\text{Pr})_3)_4$ , THF:HMPA (2:1)  
 c.- Cat.  $\text{Pd}(\text{P}(\text{O}^i\text{Pr})_3)_4$ , THF

88JA621

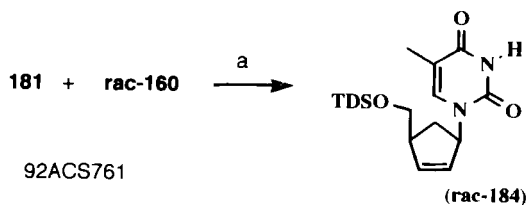
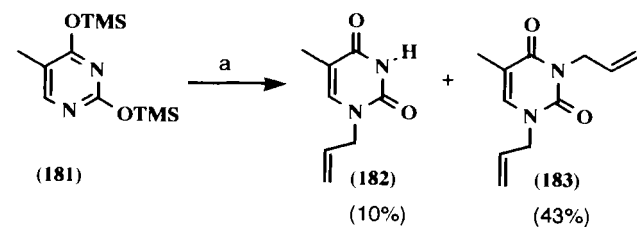
SCHEME 39



- a.- R-OCO<sub>2</sub>Me, cat.  $\text{Pd}_2(\text{dba})_3$  / dppb, THF (also DMF for 180a), 50 °C  
 b.- R-OAc, KF, cat.  $\text{Pd}_2(\text{dba})_3$  / dppb, THF, r.t.

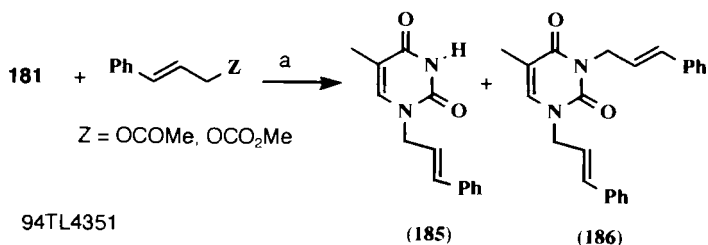
92TL8099, 94MI1, 94T10321

SCHEME 40

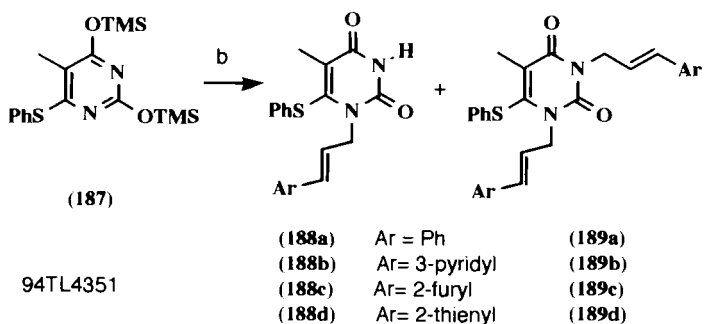


a. -  $\text{CH}_2=\text{CHCH}_2\text{OAc}$  (1 eq), cat.  $\text{Pd}(\text{OAc})_2 / \text{P}(\text{O}^i\text{Pr})_3$ ,  $\text{CH}_3\text{CN}$ , r.t.

SCHEME 41



94TL4351



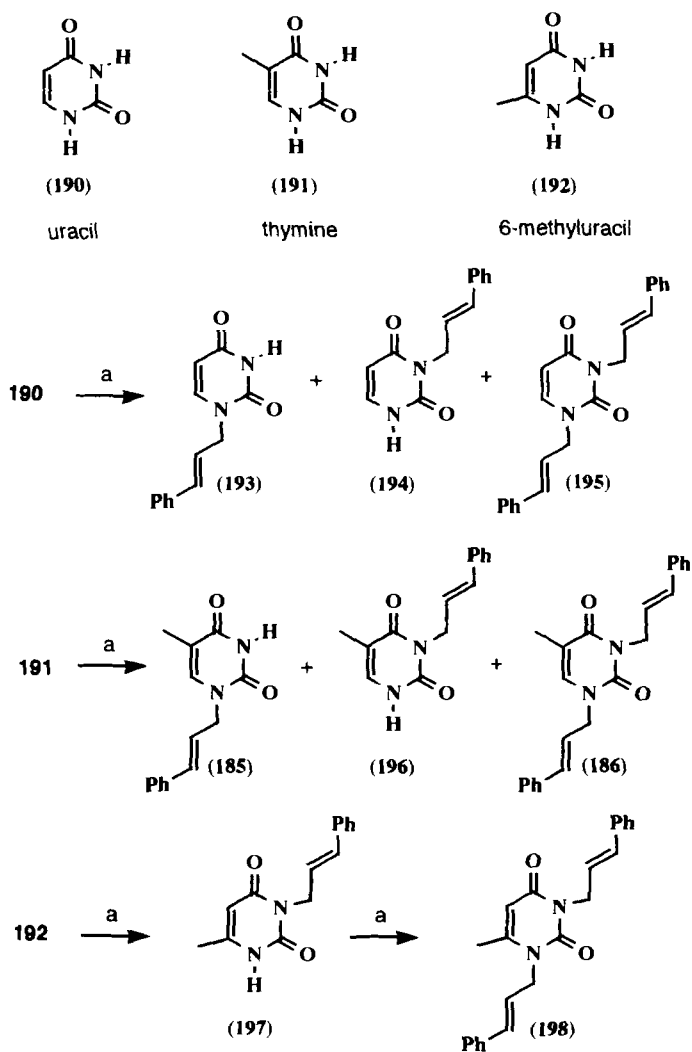
94TL4351

a. - Cat.  $\text{Pd}(\text{PPh}_3)_4$ , THF, r.t.

b. -  $\text{ArCH}=\text{CHCH}_2\text{OAc}$ , cat.  $\text{Pd}(\text{PPh}_3)_4$ , THF (or DMF), 60 °C

SCHEME 42





a. - See Table V and VI.

93T1457, 94TL7085

SCHEME 43

TABLE V  
ALLYLATIONS OF URACILS **190**–**192** AND **197**<sup>a</sup>

NuH	Precatalyst	Solvent/ <i>T</i> (°C)	N-1 (%)	N-3 (%)	N-1/N-3 (%)
<b>190</b>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	DMSO/105	<b>193</b> (38)	<b>194</b> (7)	<b>195</b> (9)
<b>191</b>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	DMSO/108	<b>185</b> (30)	<b>196</b> (14)	<b>186</b> (7)
<b>192</b>	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	Dioxane/refl.	—	<b>197</b> (52)	—
<b>192</b>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	DMSO/105	—	<b>197</b> (49)	<b>198</b> (5)
<b>197</b>	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	THF/refl.	—	—	<b>198</b> (90)

were allylated, although the regioselectivity was low, and all three possible products were generally formed: **193–195** from **190**, and **185, 186**, and **196** from **191**. In both cases, the product from allylation at N-1 was predominant. However, 6-methyluracil **192** behaves differently, regioselective allylation at N-3 (**197**) being observed. We attribute the change in regioselectivity to the steric hindrance of the C-6 methyl group which reduces the reactivity at N-1. Compound **197** was further allylated to **198** (93T1457).

Sinou and co-workers also studied the allylation of uracil **190** and thymine **191**, but in an aqueous solvent (water/acetonitrile in a ratio 17/2) and in the presence of trisodium triphenylphosphine trisulfonate (tppts, **199**) as water-soluble phosphine. Their results are summarized in Table VI. Cinnamyl acetate was used with one equivalent of diazabicycloundecene (DBU) as a base instead of mixed carbonate. Under these conditions, good regioselectivities at N-1 (to **193** and **185**) were observed, as well as lack of diallylation products for uracil and thymine, even with an excess of cinnamyl acetate. It seems that the nonformation of diallylated products is related to the precipitation of the N-1 isomers **193** and **185** in the aqueous medium (94TL7085).

Table VII summarizes additional examples of allylations of **190** and **191** as well as of cytosine **200** and 5-methylcytosine **201** (Scheme 44) with electrophiles **74**, *rac*-**166**, and *rac*-**204** together with the targeted final products. Reactions with glycoside **74** and with vinyl epoxide **204** always occur with overall retention of configuration. The reactions with cyclopentene derivatives are related to the preparation of synthetic carbanucleosides with antiviral action.

2-Thiouracil **214**, 5-methyl-2-thiouracil (2-thiothymine, **219**), and 6-methyl-2-thiouracil **224** (Scheme 45) were also studied as Pd(0)-catalyzed

TABLE VI  
ALLYATIONS OF URACILS **190** AND **191** IN AQUEOUS SOLVENTS<sup>a</sup>

NuH	R-X (number of equivalents)	Solvent	Products (%)
<b>190</b>	PhCH=CHCH <sub>2</sub> OAc (3.0)	H <sub>2</sub> O/CH <sub>3</sub> CN (17/2)	<b>193</b> (65)
<b>190</b>	PhCH=CHCH <sub>2</sub> OAc (4.0)	H <sub>2</sub> O/CH <sub>3</sub> CN (17/2)	<b>193</b> (80)
<b>190</b>	PhCH=CHCH <sub>2</sub> OCO <sub>2</sub> Et (1.1)	H <sub>2</sub> O/CH <sub>3</sub> CN (60/2)	<b>193</b> (8)
<b>191</b>	PhCH=CHCH <sub>2</sub> OAc (4.0)	H <sub>2</sub> O/CH <sub>3</sub> CN (17/2)	<b>185</b> (53)

<sup>a</sup> Cat. Pd(OAc)<sub>2</sub>/tppts, 60°C, 24 h. One equivalent of DBU is added when cinnamyl acetate is used.

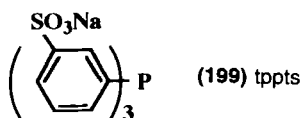
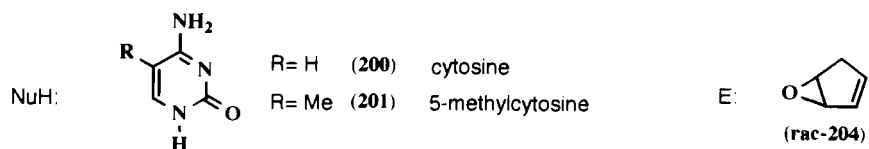
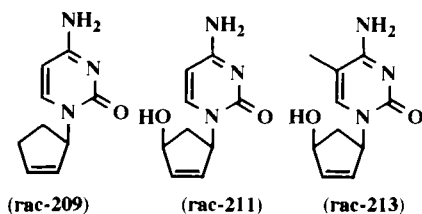
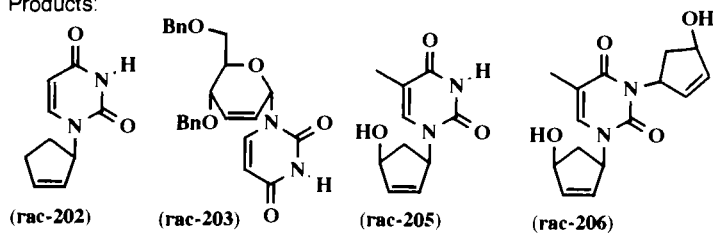


TABLE VII  
OTHER ALLYLATIONS OF URACILS **190** AND **191** AND OF CYTOSINES **200** AND **201**

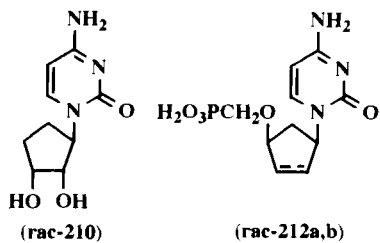
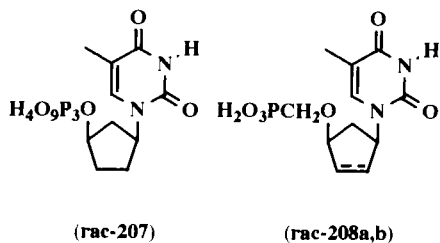
Reference	NuH	Activation/Solvent	Electrophile	Catalyst	Products	Target
92ACS686	<b>190</b>	HNa/THF	<i>rac</i> - <b>166</b>	Pd(dba) <sub>2</sub> /DPPE	<i>rac</i> - <b>202</b>	
92TL2481	<b>190</b>	—/THF	<b>74</b>	Pd <sub>2</sub> (dba) <sub>3</sub> /DPPB	<i>rac</i> - <b>203</b>	
91JCS(P1)3378	<b>191</b>	—/DMF	<i>rac</i> - <b>204</b>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	<i>rac</i> - <b>205</b> (25%)	<i>rac</i> - <b>207</b> and <i>rac</i> - <b>208a,b</b>
92JCS(P1)2695					<i>rac</i> - <b>206</b> (11%)	
92TL5335	<b>191</b>	—/THF–DMSO	<i>rac</i> - <b>204</b>	Pd(P(O <sup>i</sup> Pr) <sub>3</sub> ) <sub>4</sub>	<i>rac</i> - <b>205</b> (1%)	
93MI2					<i>rac</i> - <b>206</b> (37%)	
92ACS686	<b>200</b>	HNa/THF	<i>rac</i> - <b>166</b>	Pd(dba) <sub>2</sub> /DPPE	<i>rac</i> - <b>209</b>	<i>rac</i> - <b>210</b>
92TL5335	<b>200</b>	—/THF–DMSO	<i>rac</i> - <b>204</b>	Pd(P(O <sup>i</sup> Pr) <sub>3</sub> ) <sub>4</sub>	<i>rac</i> - <b>211</b>	<i>rac</i> - <b>212a,b</b>
93MI2						
92TL5335	<b>201</b>	—/THF–DMSO	<i>rac</i> - <b>204</b>	Pd(P(O <sup>i</sup> Pr) <sub>3</sub> ) <sub>4</sub>	<i>rac</i> - <b>213</b>	<i>rac</i> - <b>208a,b</b>
93MI2						



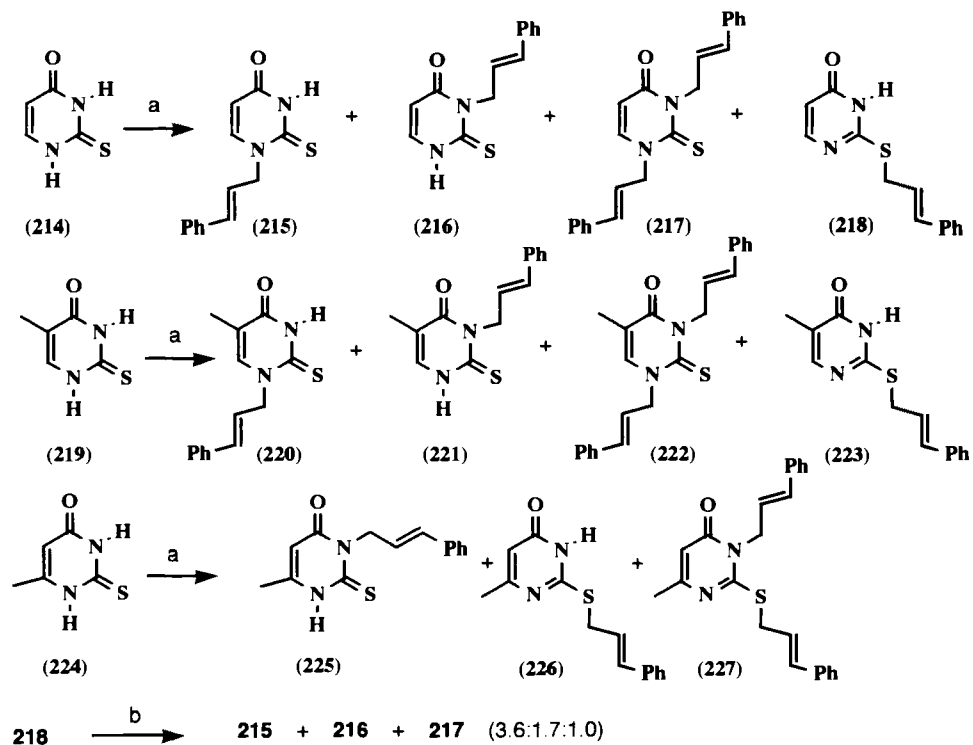
Products:



Targeted Final Products:



SCHEME 44



a. -  $\text{PhCH=CHCH}_2\text{OCO}_2\text{R}$  or  $\text{PhCH=CHCH}_2\text{OAc}$ , see Table VIII. b. - Cat.  $\text{Pd}(\text{PPh}_3)_4$ , refl. dioxane

94TL7085

SCHEME 45

TABLE VIII  
ALLYLATIONS OF THIOURACILS **214**, **219**, AND **224**

NuH	R-X (number of equivalents)	Precatalyst	Solvent/T (°C)	N-1 (%)	N-3 (%)	N-1/N-3 (%)	S (%)	S/N-3 (%)
<b>214</b>	PhCH=CHCH <sub>2</sub> OCO <sub>2</sub> Et (1.0)	Pd(PPh <sub>3</sub> ) <sub>4</sub>	dioxane/refl.	<b>215</b> (48)	<b>216</b> (14)	<b>217</b> (9)	—	—
<b>214</b>	PhCH=CHCH <sub>2</sub> OCO <sub>2</sub> Et (2.0)	Pd(PPh <sub>3</sub> ) <sub>4</sub>	dioxane/refl.	<b>215</b> (20)	<b>216</b> (23)	<b>217</b> (40)	—	—
<b>214</b>	PhCH=CHCH <sub>2</sub> OAc (5.0)	Pd(OAc) <sub>2</sub> / <b>199</b>	H <sub>2</sub> O-CH <sub>3</sub> CN (17:3)/60	—	—	—	<b>218</b> (43)	—
<b>219</b>	PhCH=CHCH <sub>2</sub> OCO <sub>2</sub> Et (1.0)	PdPPh <sub>3</sub> ) <sub>4</sub>	dioxane/refl.	<b>220</b> (23)	<b>221</b> (17)	<b>222</b> (4)	<b>223</b> (6)	—
<b>219</b>	PhCH=CHCH <sub>2</sub> OAc (5.0)	Pd(OAc) <sub>2</sub> / <b>199</b>	H <sub>2</sub> O-CH <sub>3</sub> CN (17:3)/60	—	—	—	<b>223</b> (55)	—
<b>224</b>	PhCH=CHCH <sub>2</sub> OCO <sub>2</sub> Et (1.0)	Pd(acac) <sub>2</sub> /PPh <sub>3</sub>	dioxane/refl.	—	<b>225</b> (30)	—	—	—
<b>224</b>	PhCH=CHCH <sub>2</sub> OAc (4.0)	Pd(OAc) <sub>2</sub> / <b>199</b>	H <sub>2</sub> O-CH <sub>3</sub> CN (18:2)/60	—	—	—	<b>226</b> (92)	<b>227</b> (4)

allylation substrates by Sinou and co-workers and by the current authors (94TL7085). The results are summarized in Table VIII. As in the case of the oxygenated counterparts, allylation took place, in organic solvents, at both N-1 and N-3 with low regioselectivity. Thus, **214** gave mixtures of **215**, **216**, and **217**, and the same propensity was shown by **219**. Again, the 6-methyl derivative (**224**) showed a different behavior since it gave only the product of reaction at N-3 (**225**).

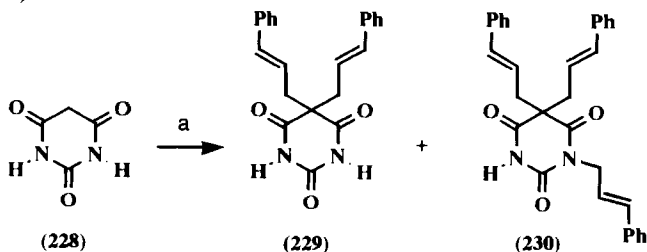
Likewise, in the case of the oxygenated analogs, the combination of the aqueous medium, the water-soluble phosphine tppts (**199**), palladium(II) acetate, and cinnamyl acetate plus DBU changed the outcome of the reaction dramatically. Thus, from **214**, **219**, and **224**, only sulfides **218**, **223** and **226** were formed. The sulfides are the products of kinetic control (see the conversion of **218** into the mixture of N-1, N-3, and N-1/N-3 allylated compounds); they separate from the reaction aqueous medium. And this fact, together with the lower temperature required when working in water/acetonitrile (17/3), permits isolation of the sulfides instead of the thermodynamically more stable *N*-allylated compounds.

#### 4. Barbituric Acid and 2-Thiobarbituric Acid

Barbituric acid **228** (Scheme 46) has been allylated, the methylene group between the carbonyls reacting first. Only when two substituents have been introduced at carbon, does the third one incorporate into a nitrogen atom as in the formation of **229** and **230** (88T7205).

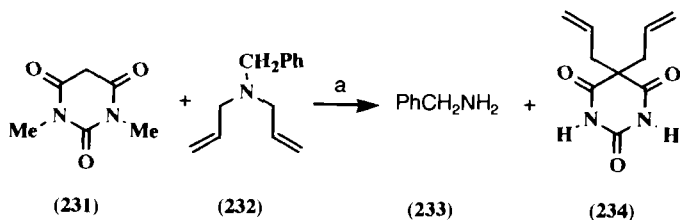
Guibé and co-workers took advantage of this high reactivity to use *N,N'*-dimethylbarbituric acid **231** (Scheme 47) as an efficient nucleophilic reagent in the deprotection of functional groups protected with allyl radicals. The recovery of benzylamine from its diallyl derivative **232** is one example (93JOC6109).

2-Thiobarbituric acid **235** (Scheme 48) also reacts first at the methylene group, then at the nitrogen atoms, as in the formation of **236** and **237** (93T1457).



a. -  $\text{PhCH=CHCH}_2\text{OAc}$ , DBU (1 eq), cat.  $\text{Pd}(\text{acac})_2 / \text{PPh}_3$ , THF, 78 °C  
88T7205

SCHEME 46



a. - Cat.  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Cl}_2\text{CH}_2$ ,  $30^\circ\text{C}$   
93JOC6109

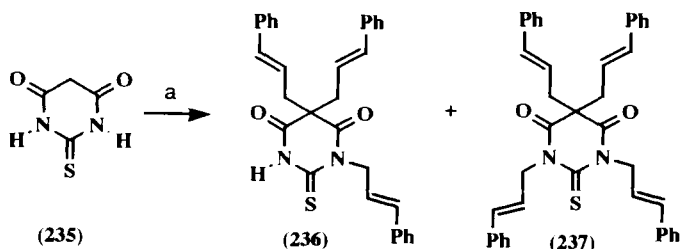
SCHEME 47

## IV. Imidazole Fused to a Second Heterocyclic Ring

### A. IMIDAZOLE FUSED TO A SIX-MEMBERED HETEROCYCLE

#### 1. Purine Bases and Related Compounds

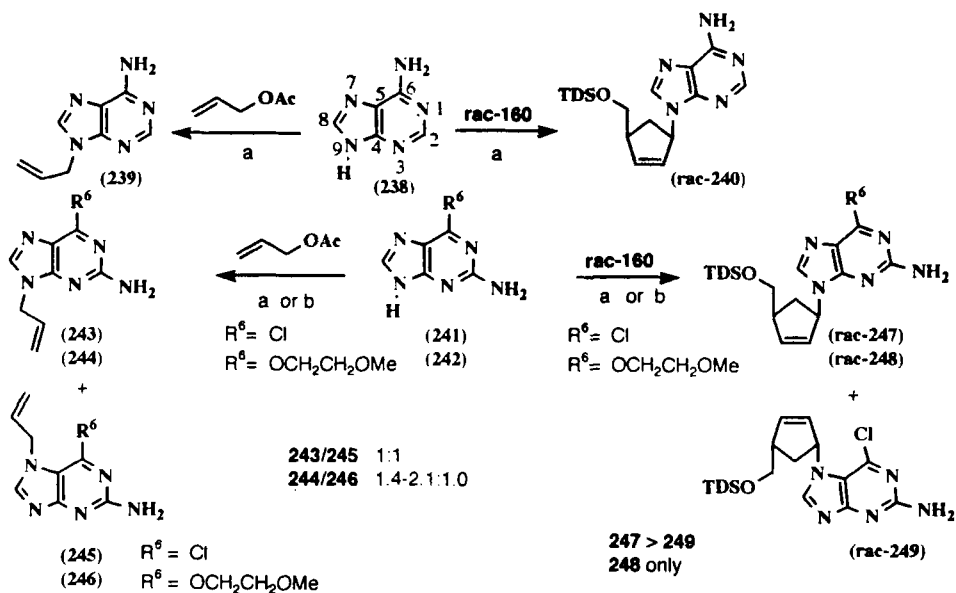
One important study on the regio- and stereoselectivity of the Pd(0)-catalyzed allylations of adenine **238** and the related 6-substituted 2-aminopurine derivatives **241** and **242** (Scheme 49) is that of Benneche and Undheim (92ACS761, 92TL1085). This group reported that adenine **238** is regioselectively allylated at N-9 both by allyl acetate and by *rac*-**160** to afford **239** and *rac*-**240** as the only isolated reaction products. However, when treated with allyl acetate, **241** and **242** afforded mixtures of *N*-allylation products at N-9 (**243** and **244**) and at N-7 (**245** and **246**). The ratios **243/245** and **244/246** indicate that the difference in reactivity between both positions is low. When both **241** and **242** were allylated with the more sterically demanding acetate *rac*-**160**, the ratio of N-9/N-7 allylation



a. -  $\text{PhCH}=\text{CHCH}_2\text{OCO}_2\text{Et}$  (3 eq), cat.  $\text{Pd}(\text{PPh}_3)_4$ , THF, r.t.  
93T1457

SCHEME 48



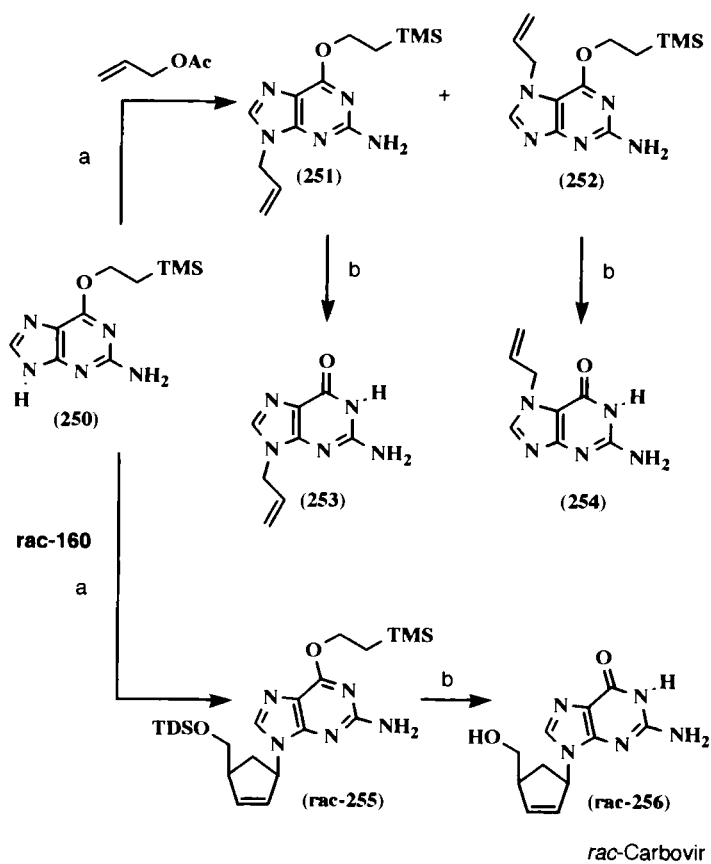


SCHEME 49

products increased. Thus, from **241**, the N-9 allylated *rac*-**247** was formed in much greater abundance than the N-7 allylated *rac*-**249**; and from **242**, only the N-9 allylation product *rac*-**248** was isolated. Therefore, the difference in reactivity between N-9 and N-7 seems to be more steric than electronic in nature, its origin being the interaction with the substituent at C-6 (92ACS761).

The same group reported the Pd(0)-catalyzed allylation of the soluble purine derivative **250**; this derivative bears at C-6 an ether that is transformed into the amide group of the final products **253**, **254**, and *rac*-**256** (Scheme 50). Again, a mixture of the N-allylation products at N-9 (**251**) and N-7 (**252**) is formed when the allylic substrate is allyl acetate, which gives a sterically undemanding cationic  $\eta^3$ -allylpalladium complex. However, the allylation with the bulkier *rac*-**160** led only to *rac*-**255**, which was further elaborated into the antiviral agent carbovir in racemic form (*rac*-**256**) (92ACS761, 92TL1085).

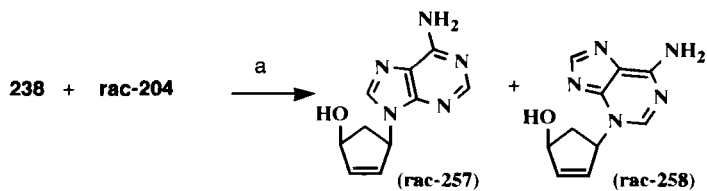
Mentions of products of allylation of positions other than N-9 have been made by Jähne and co-workers (92TL5335; 93MI2). As an example, they reported that the reaction of adenine **238** with *rac*-**204** affords *rac*-**257** and the product of allylation at N-3 (*rac*-**258**) in a 7:2 ratio (Scheme 51).



a.- HLi, cat.  $\text{Pd}(\text{PPh}_3)_4$ , DMF, 45 °C. b.-  $\text{FNBu}_4$ ,  $\text{CH}_3\text{CN}$ , 50 °C.

92ACS761, 92TL1085

SCHEME 50



257 / 258 : 7 / 2

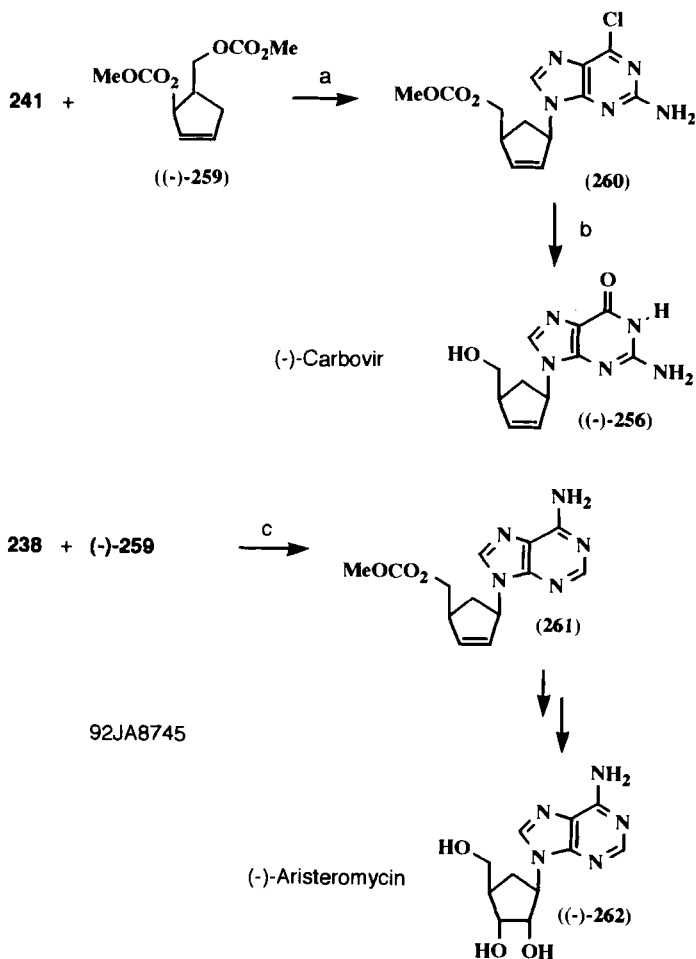
a.- Cat.  $\text{Pd}(\text{P}(\text{O}^i\text{Pr})_3)_4$ , THF-DMSO, 0 °C  $\rightarrow$  r.t.

92TL5335

SCHEME 51

Protecting the amino group at N-6 in the form of *N*<sup>6</sup>-(*N*-methyl-2-pyrroli-  
dineylidene)adenine improves the N-9 selectivity, although the yield tends  
to be lower. [For an account of the work by Jähne and co-workers see  
(93MI2).]

The interesting homochiral diol derivative (–)-**259** (Scheme 52) has been  
prepared and used by Trost and co-workers in the synthesis of the antiviral  
agents (–)-carbovir [(–)-**256**] and (–)-aristeromycin [(–)-**262**] (92JA8745).



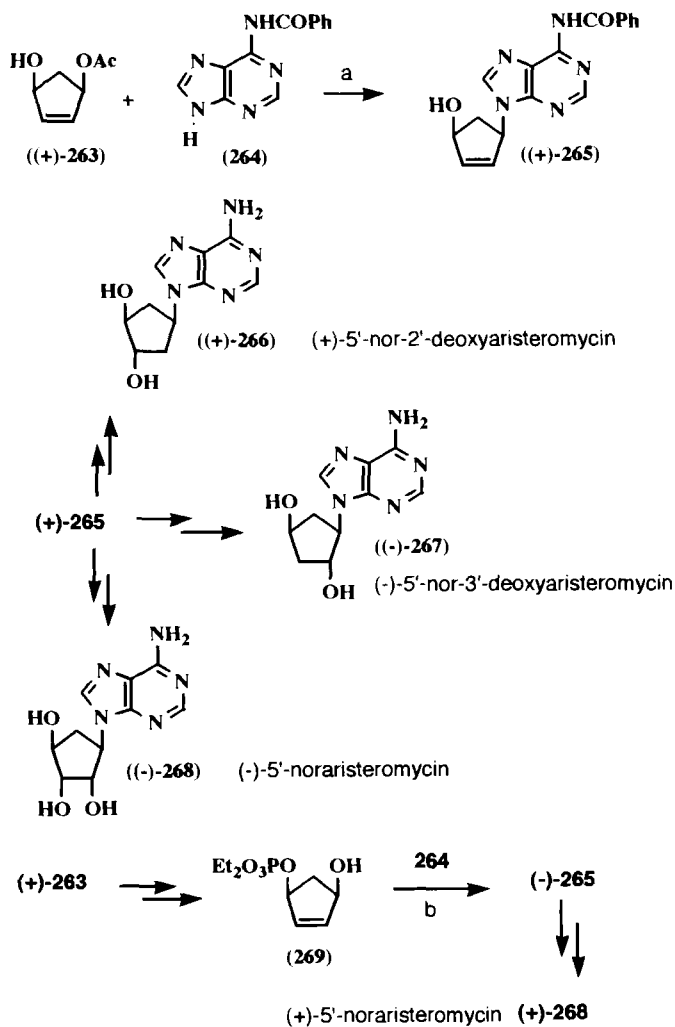
a.- Cat. ( $\text{C}_3\text{H}_5\text{PdCl}$ )<sub>2</sub> /  $\text{PPh}_3$ , THF

b.-  $\text{NaOH}$ ,  $\text{H}_2\text{O}$ , refl.

c.-  $\text{BuLi}$ , cat.  $\text{Pd}(\text{OAc})_2$  /  $\text{P}(\text{O}^i\text{Pr})_3$ , THF, r.t.

SCHEME 52

Thus, the Pd(0)-catalyzed allylation of 2-amino-6-chloropurine **241** with (–)-**259** affords **260**, which produces (–)-carbovir upon hydrolysis. A similar allylation of adenine **238** gives **261**, which on further elaboration gives (–)-aristeromycin. More recently Berranger and Langlois prepared the



a. - HNa, cat. Pd(PPh<sub>3</sub>)<sub>4</sub>, THF-DMF

b. - HNa, cat. Pd(PPh<sub>3</sub>)<sub>4</sub>, THF-DMSO

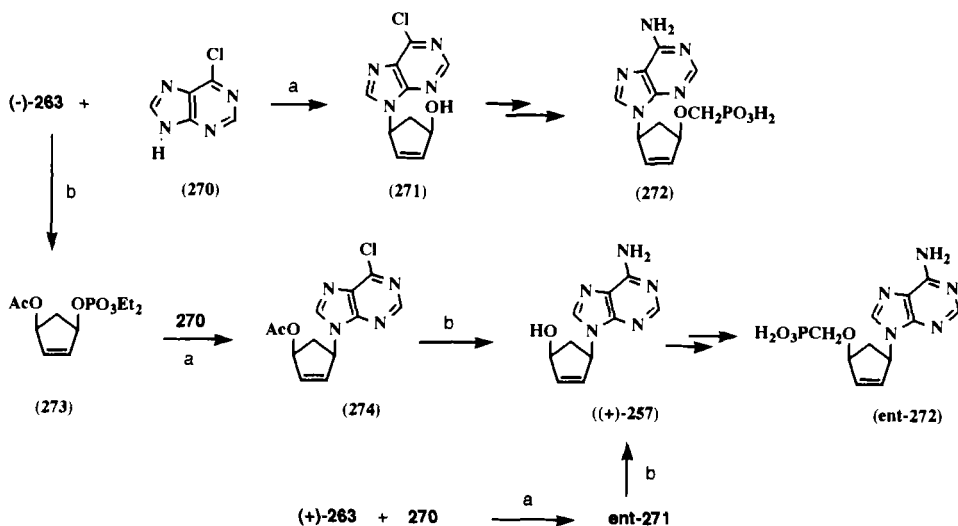
93JOC6471, 93MI3, 94JMC551

SCHEME 53

synthetic enantiomer of carbovir, (+)-**256**, from (+)-**259** by the same procedure (95TL5523).

Another very interesting homochiral diol derivative is (+)-**263** (Scheme 53), which has one less methylene group than **259**. This derivative has been used by Schneller and co-workers for the preparation of several aristeromycin derivatives (93JOC6471, 93MI3; 94JMC551). The reaction of *N*-benzoyladenine (**264**) with (+)-**263** under Pd(0) catalysis affords the key intermediate (+)-**265**, which in three different transformations was converted into (+)-5'-nor-2'-deoxyaristeromycin [(+)-**266**], (-)-5'-nor-3'-deoxyaristeromycin [(-)-**267**], and (-)-5'-noraristeromycin [(-)-**268**]. The same monoacetate (+)-**263** was converted into the homochiral diethylphosphate **269**. This is important since, under Pd(0) catalysis, (+)-**263** reacts at the carbon atom bearing the acetoxy group, whereas **269** reacts at the carbon atom bearing the phosphate moiety, thus permitting access to the enantiomeric series from just one homochiral enantiomer, (+)-**263**. This is exemplified by the reaction of **269** with **264** to afford the enantiomer (-)-**265**, which was converted into (+)-5'-noraristeromycin [(+)-**268**].

A very similar elaboration of the *levo* isomer (-)-**263** (Scheme 54) has been reported by Theil, von Janta-Lipinski, and co-workers (94TL1961; 95T761). Thus, the reaction of (-)-**263** with 6-chloropurine **270** under Pd(0) catalysis gave **271**, featuring the unusual stereochemistry characteristic of this type of carbanucleoside; then **271** was converted into the homo-



a.- HNa, cat. Pd(PPh<sub>3</sub>)<sub>4</sub>, THF, r.t. b.- MeOH, NH<sub>3</sub>

94TL1961, 95T761

SCHEME 54

chiral phosphonate **272**. However, the homochiral acetate (–)-**263** was transformed into the homochiral mixed acetate–phosphate **273**. Since a phosphate anion is a better leaving group than an acetoxy group in the Tsuji–Trost reaction, **273** reacts with **270** to afford **274**, which belongs to the usual stereochemical series. Acetate hydrolysis and substitution at C-6 converted **274** into (+)-**257**, and finally into *ent*-**272**, an enantiomer of **272**. Of course, starting with the enantiomeric homochiral acetate (+)-**263** permitted an alternative access to (+)-**257**, and hence to *ent*-**272**.

In the last few years, the Pd(0)-catalyzed allylation of purine derivatives with cyclopentene allylic systems has proved a very popular tool for preparing, ultimately, both natural and synthetic carbanucleosides in a search of products with antiviral activity. The fact that carbanucleosides are more resistant to enzymatic hydrolysis than conventional nucleosides further explains the current interest in this field. On the other hand, the antiviral activity could be associated with carbanucleotide structures rather than carbanucleosides—hence the rising interest in the preparation of triphosphates of carbanucleosides. But triphosphates are difficult to prepare, so this interest has been extended to phosphonates. Much easier to prepare, phosphonates are isosteric of phosphates, and they cannot be hydrolyzed at the C–P bond. Sometimes, the cyclopentene moiety has only ring carbon atoms, so that such starting materials as cyclopentadiene epoxide **204**, acetate **166**, and homochiral acetates **263** are required. In other cases, however, the cyclopentene ring has an additional carbon atom at C-5', so that starting materials such as diacetates **68** and **69**, acetate silyl ethers **72** and **160**, homochiral dicarbonate **259**, and homochiral acetoxy ethers **277** and **278** are needed. Functionalized cyclopentene bearing two additional carbon atoms have been also reported (94JOC7214). Additional reactions are generally performed at the allylic double bond to reach the targeted structures.

In Table IX we cross-reference all combinations of nucleophiles and electrophiles known to the authors of this review. Nucleophiles include **238**, **241**, **270**, **275**, and **276**; and electrophiles include *rac*-**166**, *rac*-**204**, (+)-**263**, *rac*-**68**, *rac*-**72**, (–)-**277**, (+)-**278**, *rac*-**279–282**, and **74**. (See also Scheme 55.) The table is ordered by increasing numbering of final product. Formulas of final products *rac*-**283** through **297** are not included, since they can be deduced from the crossings; however *rac*-**295**, which cannot be deduced, is given.

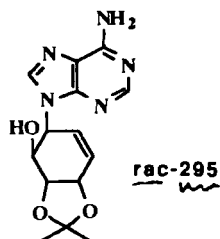
## 2. Deazapurine Bases and Related Compounds

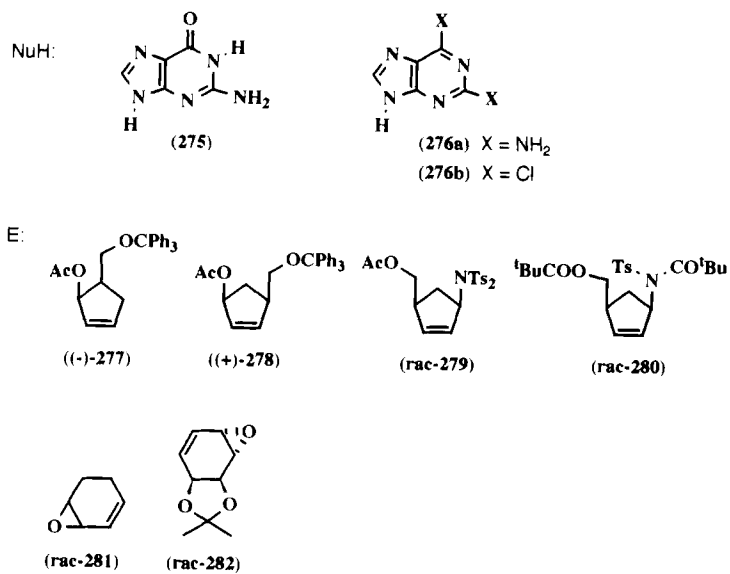
The Schneller group has reported the Pd(0)-catalyzed reactions of homochiral acetate (+)-**263** with imidazopyridine **298** to give **299** (95JMC1035) and with pyrrolopyrimidine **300** to give **301** (93MI3), as shown in Scheme 56.

TABLE IX  
OTHER ALLYATIONS OF PURINE DERIVATIVES

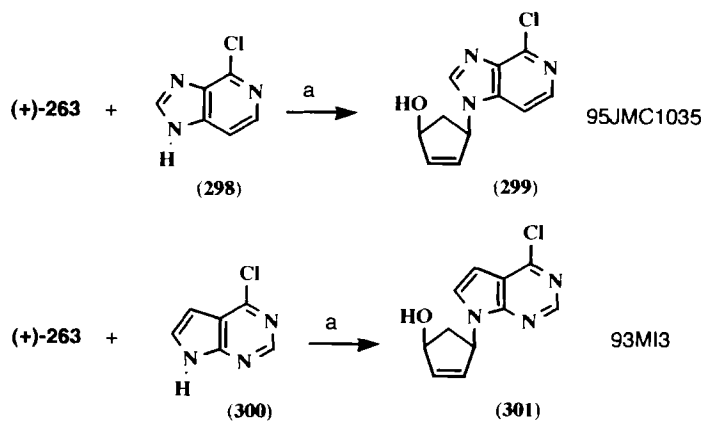
	238	241	270	275	276a,b
<i>rac</i> -166	<i>rac</i> -283 92ACS686	—	—	<i>rac</i> -284 92ACS686	—
<i>rac</i> -204	<i>rac</i> -257 88JA621 <sup>a</sup> 93JCS(P1)1717 <sup>b</sup>	<i>rac</i> -285 91JCS(CC)312 91JOC4990 <sup>f</sup> 92JCS(P1)2695 92TL5335 93JCS(P1)1717 <sup>b</sup> 94JCS(P1)1477 <sup>b</sup>	<i>rac</i> -271 93JCS(P1)1717 <sup>b</sup> 93MI2	<i>rac</i> -284' 93MI2	—
(+)-263	(+)-257 93TL6745	(+)-285 91JOC4990	—	—	285' (X = Cl) 95JMC1174
<i>rac</i> -68	<i>rac</i> -286 91JCS(P1)2603 <sup>a</sup>	<i>rac</i> -287 94JCS(P1)3373	—	—	<i>rac</i> -288 (X = NH <sub>2</sub> ) 94JCS(P1)3373
<i>rac</i> -72	<i>rac</i> -289 91JCS(P1)2605 <sup>a</sup>	—	—	—	—
(-)-277	—	290 93JCS(P1)313 <sup>c</sup>	—	—	—
(+)-278	—	<i>ent</i> -290 91JCS(P1)2605 <sup>d</sup> 92JCS(P1)589	291 91JCS(P1)2605 <sup>e</sup>	—	—
<i>rac</i> -279	—	<i>rac</i> -292 94JOC4719 <sup>f</sup>	—	—	—
<i>rac</i> -280	—	<i>rac</i> -293 94JOC4719 <sup>f</sup>	—	—	—
<i>rac</i> -281	<i>rac</i> -294 92JOC5861	—	—	—	—
<i>rac</i> -282	<i>rac</i> -295 92JOC5861	—	—	—	—
74	296 92TL2481	—	297 92TL2481	—	—

<sup>a</sup> In a synthesis of *rac*-aristeromycin (*rac*-262). <sup>b</sup> Enzymatic resolution of the product. <sup>c</sup> In a synthesis of (-)-carbovir [(-)-256]. <sup>d</sup> In a synthesis of (+)-carbovir [(+)-256]. <sup>e</sup> In a synthesis of (+)-aristeromycin [(+)-262]. <sup>f</sup> In a synthesis of *rac*-carbovir (*rac*-256).





SCHEME 55

a - HNa, cat. Pd(PPh<sub>3</sub>)<sub>4</sub>, THF, r.t.

SCHEME 56





**SCHEME 58**

## ADDENDUM

After the numbering of the formulas given in this review was already complete, we found an article by Monneret, Florent, and co-workers who reported the Pd(0)-catalyzed reactions of glycal **304** with 2,4-bis(trimethylsilyloxy)thymine **181** to afford **305**, and with the *O*-trimethylsilyl derivative of cytosine **306** to afford **307** (95TL3523), as shown in Scheme 58.

## ACKNOWLEDGMENTS

The financial support of DGICYT (Ministry of Education and Science of Spain) (Project PB93-0896) and CIRIT (Generalitat de Catalunya) (GRQ93-2011) is gratefully acknowledged. The initial steps of this review were taken during the tenure of one of us (M.M.-M.) as *Professeur Invité* at the Université Claude Bernard (LYON I) at Villeurbanne (France). M.M.-M. thanks the French Ministère de l'Enseignement Supérieur et de la Recherche and Professor Denis Sinou for his hospitality.

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## Chemistry of 1,3-Thiazin-4-ones and Their Derivatives

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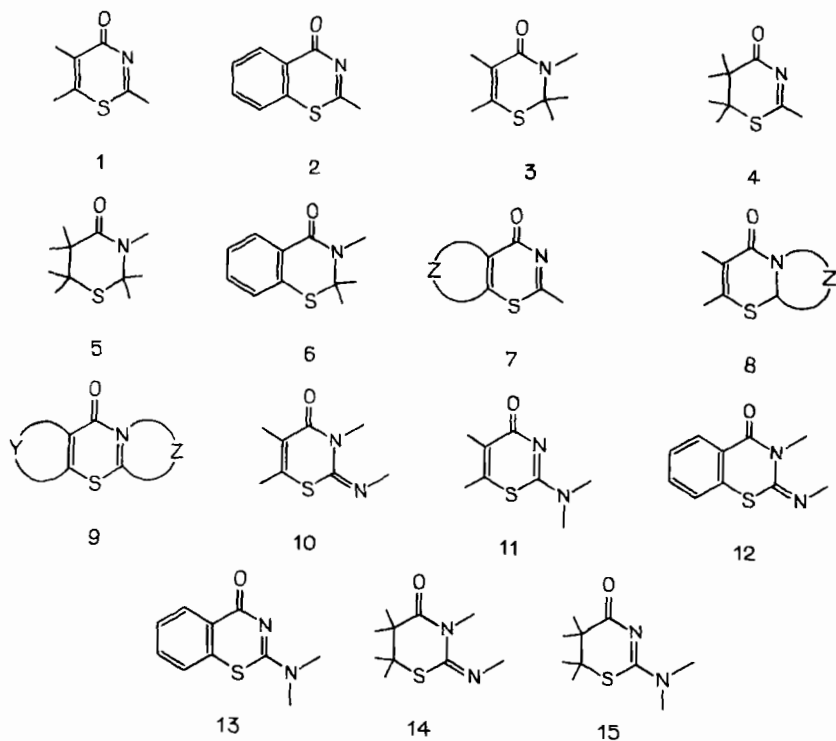
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## I. Introduction

Since the middle of the 1960s, 1,3-thiazin-4-ones (later referred to as TAs) have been the subject of intensive work owing to the uniqueness of their chemistry and the significant biological activity of many of these compounds.

Despite the large number of papers published on the chemistry of TAs, these heterocycles have not yet been reviewed separately. There is some information on TAs in reviews on 1,3-thiazines (79MI1; 84MI1). More complete information on the chemistry of 4-oxo derivatives may be found in other reviews (79KGS291; 86KGS3), but the chemical transformations of the heterocyclic ring considered therein are not systematized into groups of derivatives or types of reactions.

The present review deals with the chemistry of the structures presented in Scheme 1. The organization of material follows the sequence of formulas



Y, Z = Heterocyclic rings

SCHEME 1

**1–9.** The 2-imino-TAs **10**, **12**, and **14** are considered together with their 2-amino tautomers **11**, **13**, and **15**. However, the data on compounds **10–15** is placed at the end of each section because of the specific character of their chemistry.

Data on 1,3-thiazine-2,4-diones and their thioxo analogs are not included in this article because the number of references on these compounds is too large. These compounds should be the subject of an independent review.

## II. Syntheses

Traditionally, the methods of TA syntheses have been classified according to the number of atoms included in the fragments used for the construction of the heterocyclic ring (70AJC51; 86KGS3). In our view, this classification seems to be less than ideal because it does not take into consideration the structure of the starting compounds. However, both the availability and structure of the starting materials are undoubtedly important in choosing a synthetic method. That is why we have tried to group papers on each class of TA by starting with the structures of the initial compounds, then illustrating analogous reactions in general schemes.

### A. 1,3-THIAZIN-4-ONES

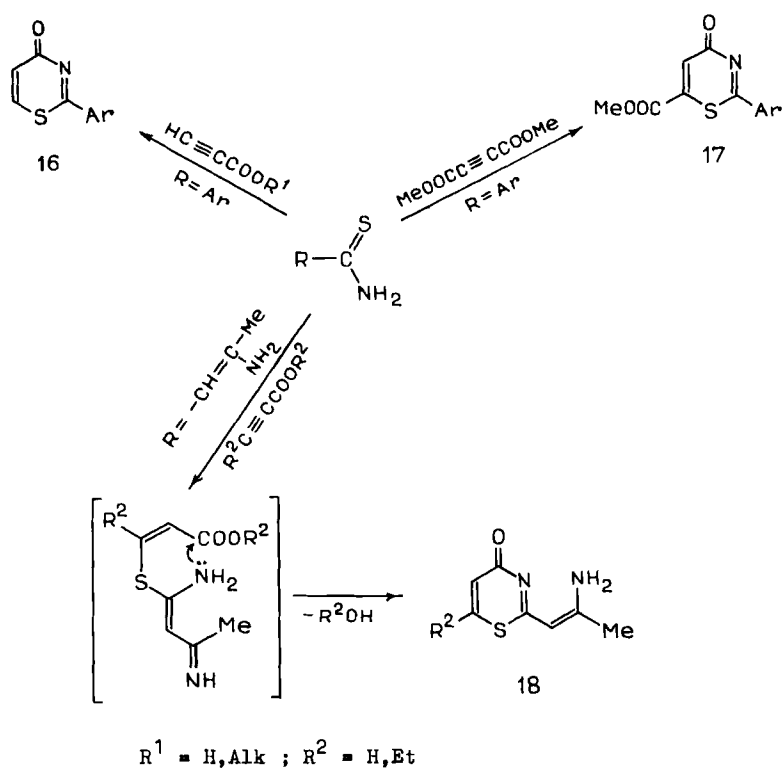
One of the most widely used methods of synthesizing TAs **16** and **17** is by condensation of thiobenzamides with acetylene mono- and dicarboxylic acids or their esters in methanol. The analogous reaction between enaminothioamide and acetylene carboxylic acid and its esters leads to enamino-TA **18** (79JAP79 20504) (Scheme 2).

The thermal condensation of dithiooxamide with trichlorophenyl malonates results in thioamide **19**, which with an excess of malonate gives a symmetric bis-TA **20**. With other carbonyl compounds, thioamide **19** may be converted into other TAs with heterocyclic substituents, **21** and **22** (73JHC223) (Scheme 3).

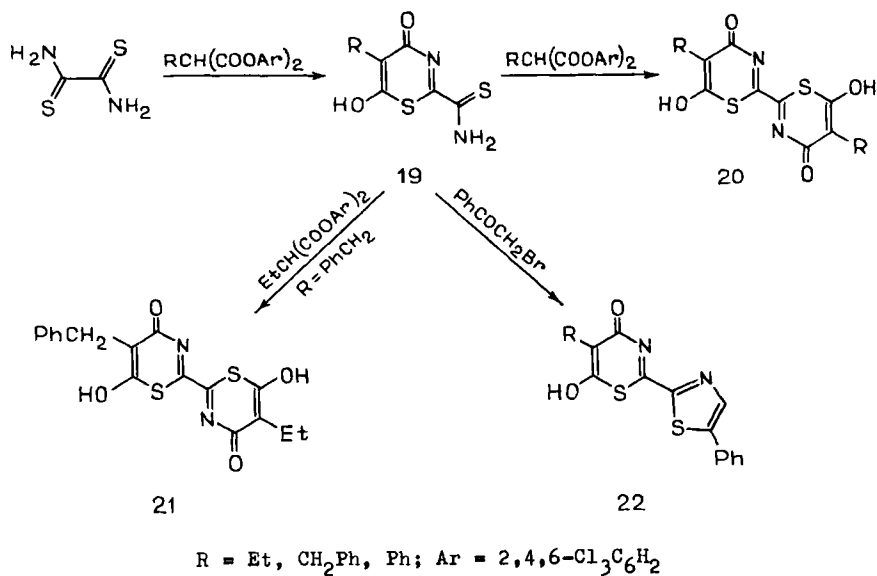
Thiobenzoyl isocyanate is widely used as a starting material for the syntheses of TAs **23–28** both in condensation with ethyl sodiocyanoacetate (86KGS3) and in [4 + 2]-cycloaddition reactions with alkenes and alkynes containing electron-donor groups (81CB2713; 85ZC324) (Scheme 4). It is established that the rate of cycloaddition increases from alkenes to alkynes and with the electron-donor properties of substituents.

The condensation of ketene-*S,S*-hemiacetal **29** with aryl cyanates leads to 2-aryloxy-TA **30** (85ZC430) (Scheme 5).

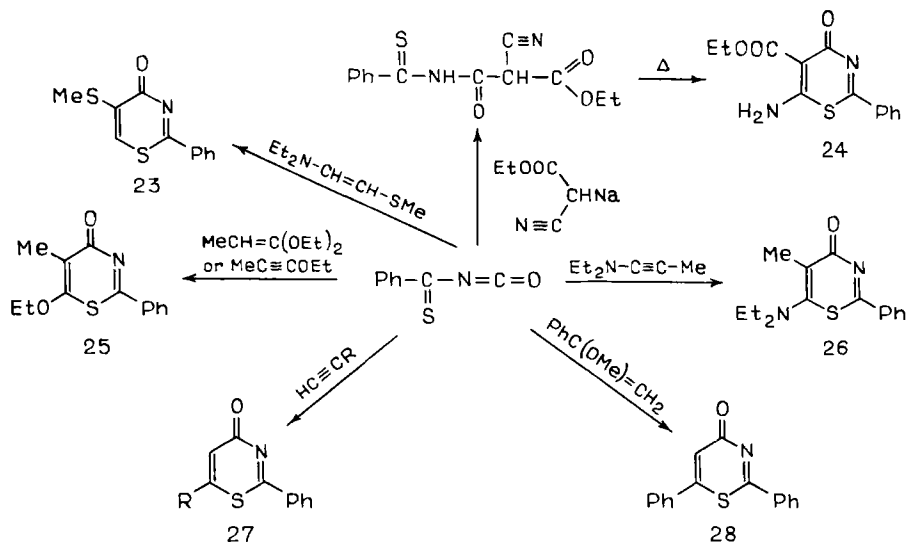




SCHEME 2



SCHEME 3



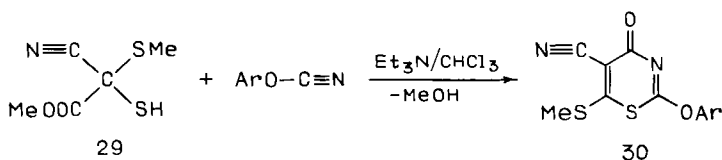
R = OEt, SMe

SCHEME 4

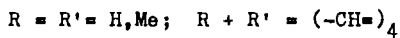
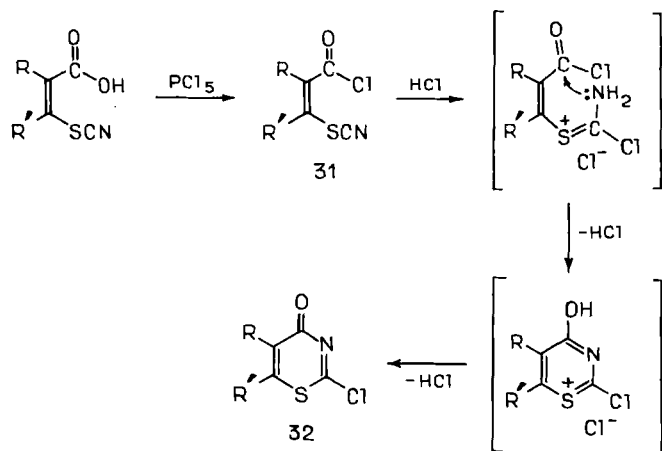
A number of methods of TA synthesis are based on the cyclization of previously prepared six-membered fragments. Thus, chloroanhydrides **31** were transformed into 2-chloro-TA **32** (72GEP2010558; 77LA1249) (Scheme 6).

For the synthesis of 2-alkylthio-TA **36**, several methods based on the cyclization of dithiourethanes (**33**, **34**, and **35**) are suggested (66TL3225; 70AJC51; 82CCC3268). Compounds **34** are intermediates, but dithiourethanes **33** and **35** were first isolated, then introduced into the cyclization reaction (Scheme 7).

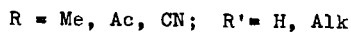
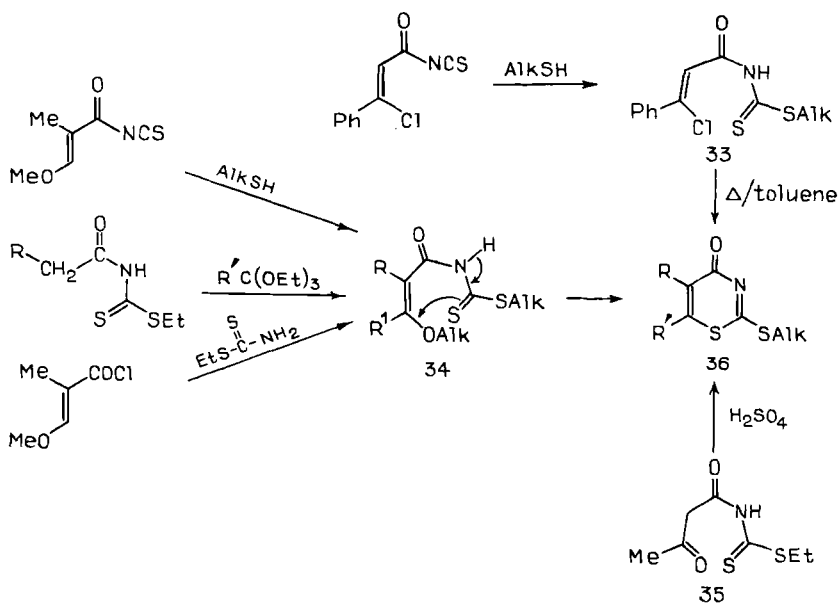
An important method of synthesizing TA **39** is based on the consecutive reactions of *N*-acetoacetylcarboxamides first with strong acids (70%  $\text{HClO}_4$ ,

Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>

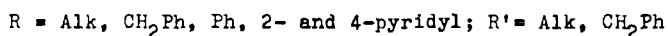
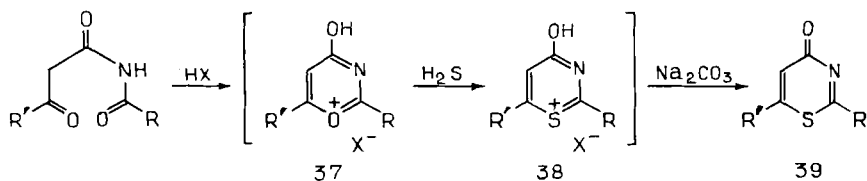
SCHEME 5



SCHEME 6



SCHEME 7



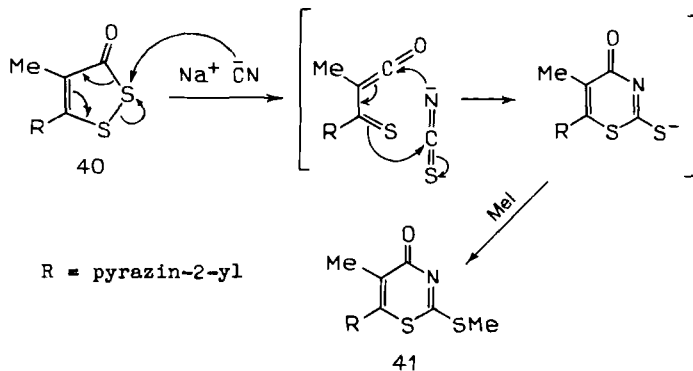
SCHEME 8

FSO<sub>3</sub>H, ClSO<sub>3</sub>H, HBF<sub>4</sub>), then with hydrogen sulfide, and then with an alkaline solution (81H851; 83CPB1929). The authors postulate in this sequence the formation of azapyrylium **37** and thioazapyrylium **38** cations (Scheme 8).

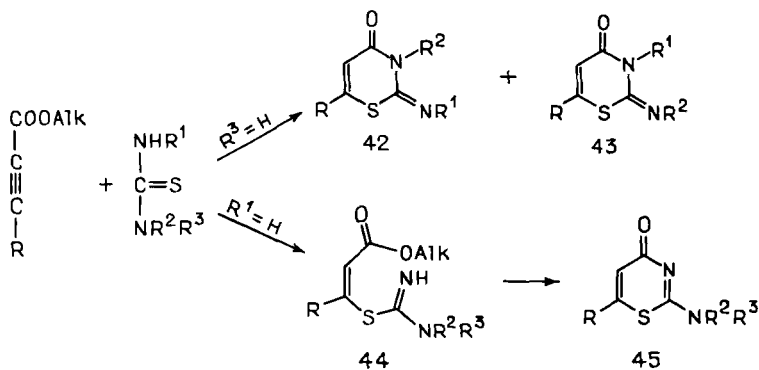
An unusual synthesis of 2-alkylthio-TA **41** consists in the ring enlargement of 1,2-dithiole-3-thiones **40** in the reaction with sodium cyanide, followed by methylation (88JHC1223) (Scheme 9). The suggested mechanism is confirmed by an increase in yield of TA **41**, when excess thiocyanate ion is added.

**2-Imino or 2-amino Derivatives.** The principles behind the syntheses of 2-amino(or 2-imino)-substituted TAs do not differ greatly from those of other TAs. Their peculiarity consists in the type of reagents used to provide the amino or imino group.

For the syntheses of 2-amino(or 2-imino)-TAs **42**, **43**, and **45** the condensation of acetylenic esters with thiourea and their *N*-alkyl derivatives is used most often [62CPB19; 64CPB683; 67CB3671, 67CJC939; 68CPB1351,



SCHEME 9



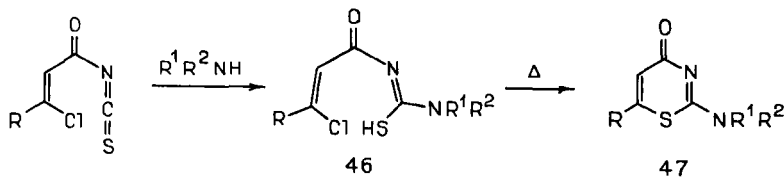
$\text{R} = \text{COOMe}, \text{Ar}, 2\text{-furyl}$ ;  $\text{R}^1 = \text{H}, \text{Alk}, \text{Ar}$ ;  $\text{R}^2 = \text{H}, \text{Alk}, \text{Ar}$ ;  $\text{R}^3 = \text{H}, \text{Alk}$

SCHEME 10

68JCS(C)2510; 69JOU621; 78JCS(P1)1428]. The first step is a nucleophilic addition of a sulfur atom to the acetylenic bond. In some cases intermediates **44** were isolated (74CS35) (Scheme 10).

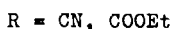
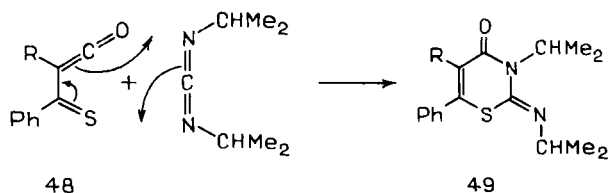
The analogous condensation of methyl acetylenedicarboxylate with substituted thiosemicarbazides leads to 2-imino-3-amino-6-carbomethoxyl-1,3-thiazin-4-ones (67CJC953).

2-Amino derivatives of TA have been obtained by using acyl isothiocyanates containing a  $\beta$ -chlorovinyl group. Other components of the reaction were primary and secondary aliphatic, aromatic (82CCC3268), and heterocyclic (82GDP149807) amines. The first step of this reaction is the formation of substituted thioureas **46**. The succeeding cyclization in boiling toluene gives TAs **47** (Scheme 11).



$\text{R} = \text{Ph}, \text{Me}$ ;  $\text{R}^1 = \text{Alk}, \text{CH}_2\text{Ph}, \text{Ph}$ ;  $\text{R}^2 = \text{H}$ ;  $\text{R}^1 + \text{R}^2 =$

SCHEME 11



SCHEME 12

Cycloaddition of thiobenzoylketenes **48** and diisopropylcarbodiimide results in imino-TAs **49** (76TL2961) (Scheme 12).

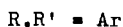
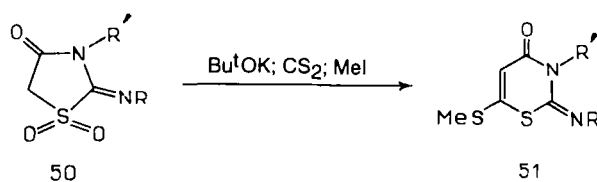
Some methods are based on the enlargement of five- or four-membered heterorings. Thus, thiazole-1, 1-dioxides **50** were transformed into 2-imino-TAs **51** by a reaction with carbon disulfide, methyl iodide, and potassium *tert*-butoxide (75GDP108991, 75ZC480) (Scheme 13).

The recyclization of thiadiazolium betaines **52** in acetic anhydride gave TAs **53** (92KGS1680; 93KGS263) (Scheme 14).

The ring transformation of thiazetidine **54** by the action of diethylaminopropyne gives 2-imino-TAs **55** (82BSB243; 83BSB61) (Scheme 15).

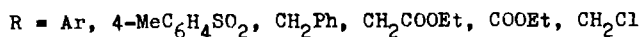
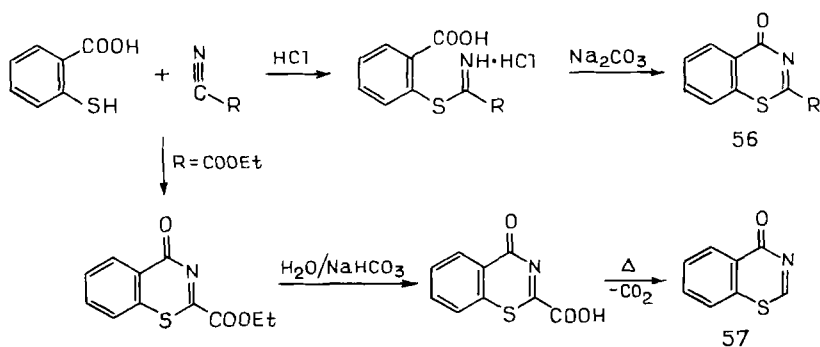
### B. 1,3-BENZOTHAZIN-4-ONES

*From 2-mercaptobenzoic Acid.* The most widely used method of 1,3-benzo-TA synthesis is the reaction of 2-mercaptobenzoic acid with compounds containing a cyano group to afford various 2-substituted 1,3-benzo-TAs **56** [aryl and benzyl (57MI1), chloromethyl, and carboethoxymethyl (60MI1)]. Note that nitriles of aliphatic acids (acetonitrile and others) do not react in these conditions. The reaction of 2-mercaptobenzoic acid with



SCHEME 13

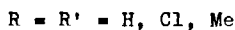
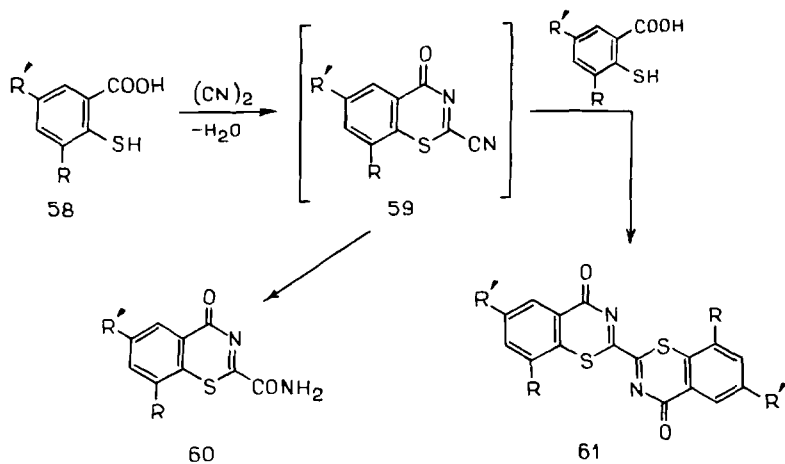




SCHEME 16

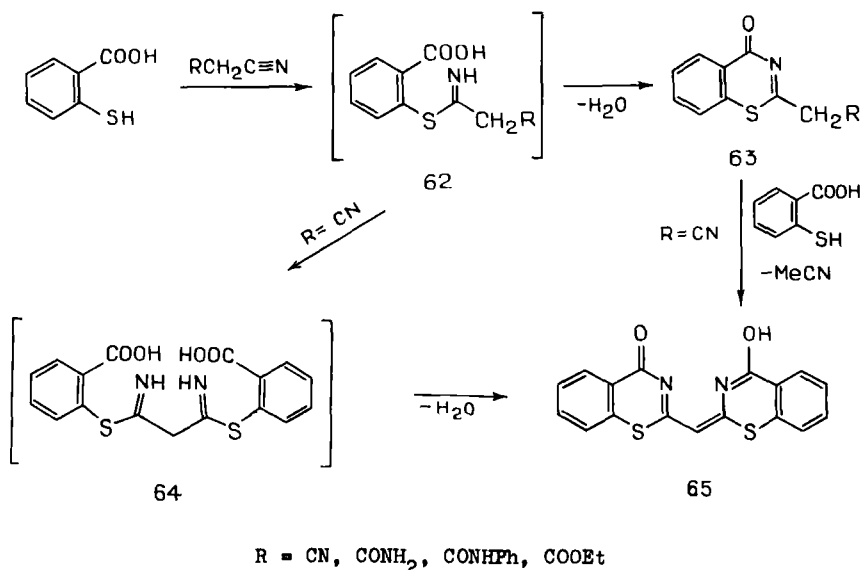
or that **62** may be transformed by self-condensation into intermediate **64**, whose subsequent cyclization gives the same bis product (84H1677) (Scheme 18).

Cyanates may also be used for the formation of the thiazinone ring, in which case the other component of this reaction is either 2-mercaptobenzoic



SCHEME 17



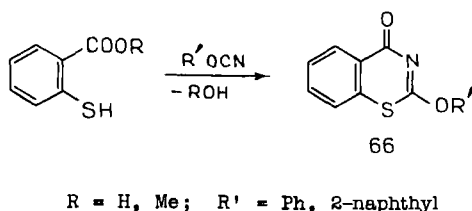


SCHEME 18

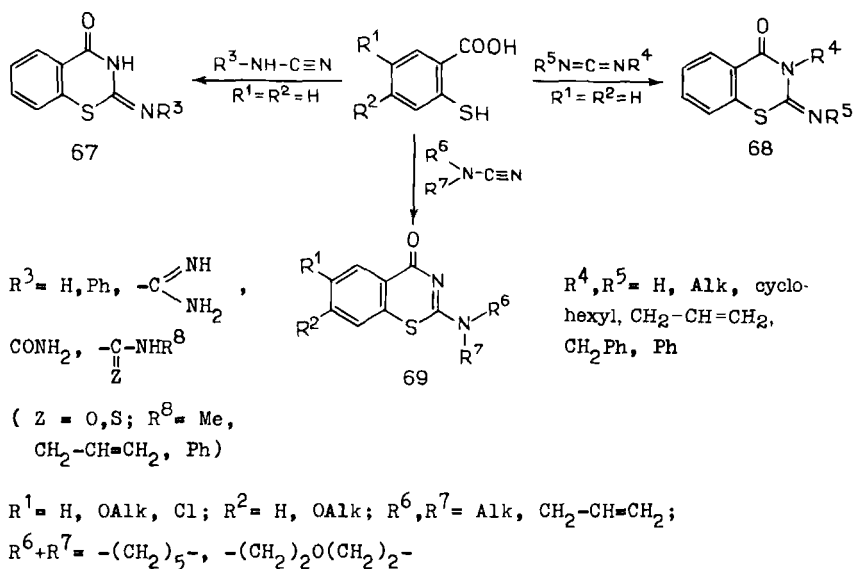
acid or its methyl ester (64CB3036; 71GEP1302657). Benzo-TAs **66** were prepared in this way (Scheme 19).

The reaction of 2-mercaptobenzoic acid derivatives with various aminonitriles or carbodiimides has been widely used for the syntheses of imino- or amino-1,3-benzo-TAs **67**, **68**, and **69**. Studies have been carried out on the reactions with cyanamide (61GEP1096361, 61USP2978448; 63ZOB213), phenylcyanamide (67PHA611), dialkylcyanamides (69GEP1807165; 69USP3470168), cyanourea and cyanothiurea (64ZOB1307; 73KGS644), and carbodiimides (62JOC3365; 64USP3149106) (Scheme 20).

As a rule, the interaction of functionally substituted nitriles with 2-mercaptobenzoic acid takes place at the expense of the cyano group's



SCHEME 19



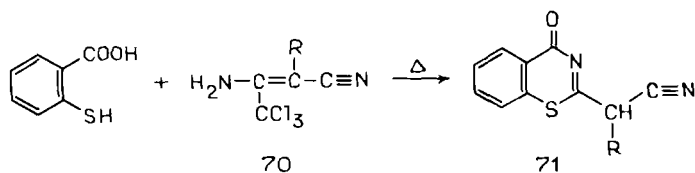
SCHEME 20

inclusion into the heterocycle. An exception to this rule is the reaction of the acid with nitrile **70**. Formation of the benzo-TA **71** heterocyclic ring includes the elimination of chloroform (88CIL563) (Scheme 21).

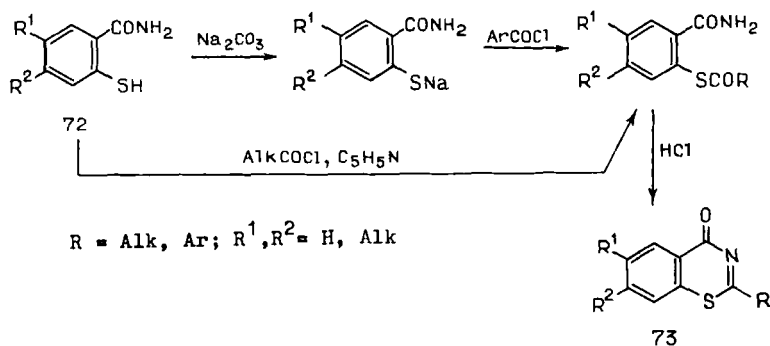
*From 2-mercaptobenzamides.* This group of syntheses includes *S*-acylation of starting amides **72**, followed by cyclodehydration to 6,7-disubstituted benzo-TAs **73** (53AP437; 58ACH201) (Scheme 22).

The reaction of zinc salt **74** with benzotrichloride was used for the synthesis of 1,3-benzo-TA **76** and may include the formation of cation **75** as an intermediate (59BSF1791) (Scheme 23).

2-Iminobenzo-TA may also be obtained from *N*-substituted amides **77**. Trifluoro derivatives **78** with fungicidal activity were obtained by a reaction



SCHEME 21



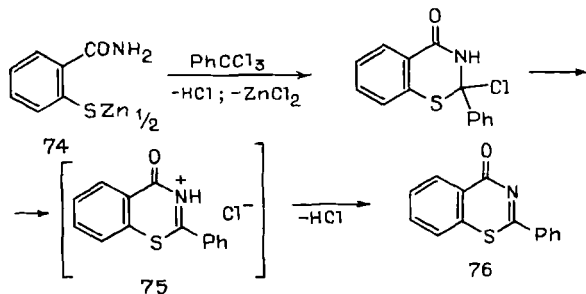
SCHEME 22

with perfluoroazapropene (74GEP2218301). 2-Mercaptobenzhydrazide reacts with cyanogen to give the imine **79** (75MI1) (Scheme 24).

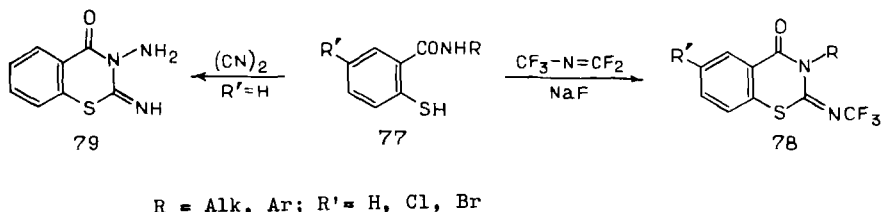
*From 2-thiocyanobenzoic Acids.* For the synthesis of 2-chlorobenzo-TA **83**, a method based on the cyclization of chloroanhydrides **80** was developed. The reaction may include the formation of heterocyclic cations **81** or **82**, whose deprotonation results in 2-chloro products **83** (66AGE663; 70CB413) (Scheme 25). Following this development, the one-pot syntheses of 2-chlorobenzo-TA, without isolation of chloroanhydrides **80**, were elaborated (73S189; 89MI1).

*From 4H-1,3-benzothiazines.* 2-Arylbenzo-TAs **85** may be synthesized via oxidation of thiazines **84** by means of chromic anhydride (58ACH201) or potassium permanganate (89MI1) (Scheme 26).

*From Derivatives of 2-halogenobenzoic Acids.* The syntheses of the previously described benzo-TAs are based on the use of various 2-mercaptobenzoic acid derivatives. In addition, some researchers have reported the use of nucleophilic aromatic substitution of a halogen atom by a sulfur



SCHEME 23

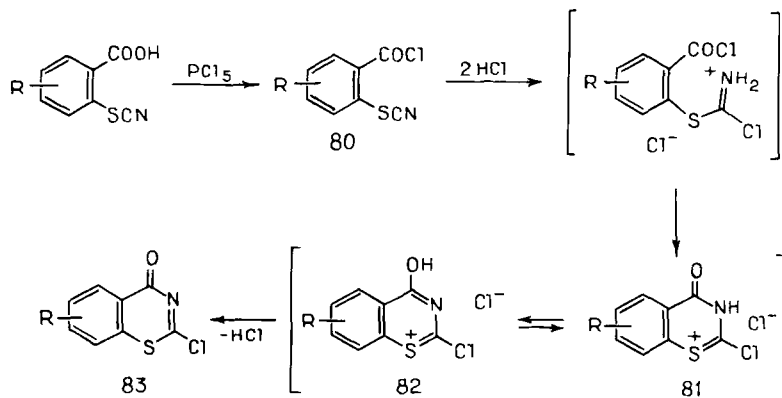


SCHEME 24

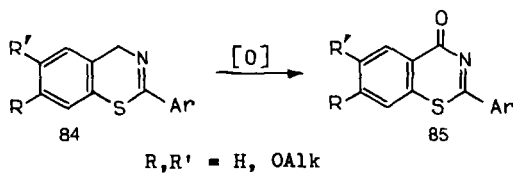
nucleophile in starting 2-halogenobenzoic acid derivatives as a key step. Thus, for example, 2-iminobenzo-TAs **87** have been obtained from chloroesters **86** and thioureas (65JIC97) (Scheme 27).

A similar reaction has been more recently described by other authors. Thioureas **89**—the intermediates in the preceding reaction—were prepared from isothiocyanate **88** and amines. Benzo-TAs **90**, which contain substituents on the exocyclic nitrogen atom, were obtained (92MI1) (Scheme 28).

These two reactions are limited by the fact that a nitro group must be present on the benzene ring to facilitate the elimination of the chlorine atom. However, this restriction may be removed by the use of a transition-metal complex—most often, a nickel(0) catalyst. The starting compounds are 2-iodobenzoic acid derivatives **91** (amides, nitriles, and esters) and *N,N*-disubstituted thioureas. In this case, electron-acceptor groups in the benzene ring are not obligatory; the reaction is general and allows one



SCHEME 25



SCHEME 26

to obtain a number of different imines **92** (90CL2205; 93JAP92/275280) (Scheme 29).

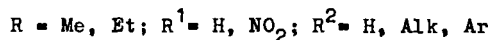
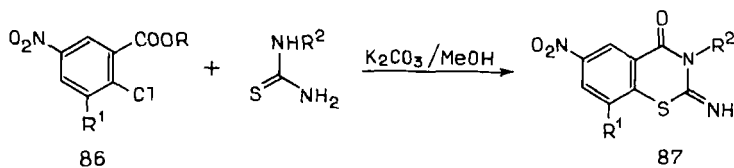
*From Isothiazolium Salts and Other Reactions.* An interesting synthesis of benzo-TA is based on recyclization of chlorothiazolium salts **93** by the action of formamides. The quantitative yield of products depends on the formamide used and the reaction conditions. If  $R'$  is a sterically encumbered group ( $\text{Me}_2\text{CH}$ ,  $\text{Me}_3\text{C}$ , or  $\text{Ph}$ ), benzo-TAs **94** are formed, while other formamides give isomers **95**. With 1,2-dichlorobenzene, only the isomers **94** were obtained. The regioselectivity of this reaction was explained by the position of nucleophilic attack of the formamide (71CB3757) (Scheme 30).

A similar reaction was observed, when isothiazole **96** was heated in dimethylformamide (DMF) (72JAP72/17781). Other 2-aminobenzo-TAs **97** were obtained via dechlorination of *N*-aroylchloroformamidines **98** by the action of phenylhydrazine (82CB1662) (Scheme 31).

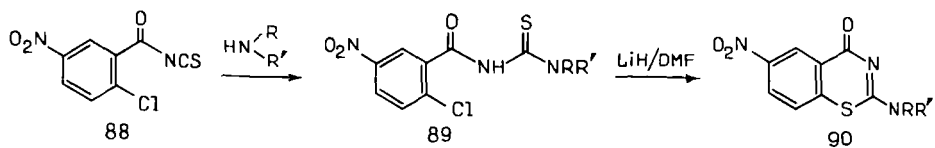
## C. REDUCED 1,3-THIAZIN-4-ONES

### 1. 2,3-Dihydro-1,3-thiazin-4-ones

The syntheses of 2,3-dihydro-TAs are the least developed. A few reactions are based on the ring enlargement of isothiazolones. The rearrange-



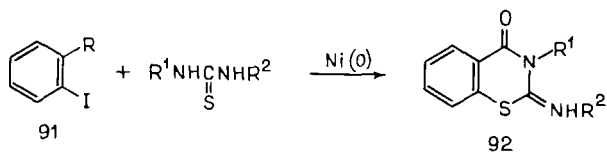
SCHEME 27



$\text{R} = \text{H}; \text{R}' = \text{H}, \text{Et}, \text{Ph}, \text{CH}_2\text{Ph}, \text{CH}_2\text{CH}_2\text{Ph}; \text{R} = \text{R}' = \text{Et}, \text{Ph};$

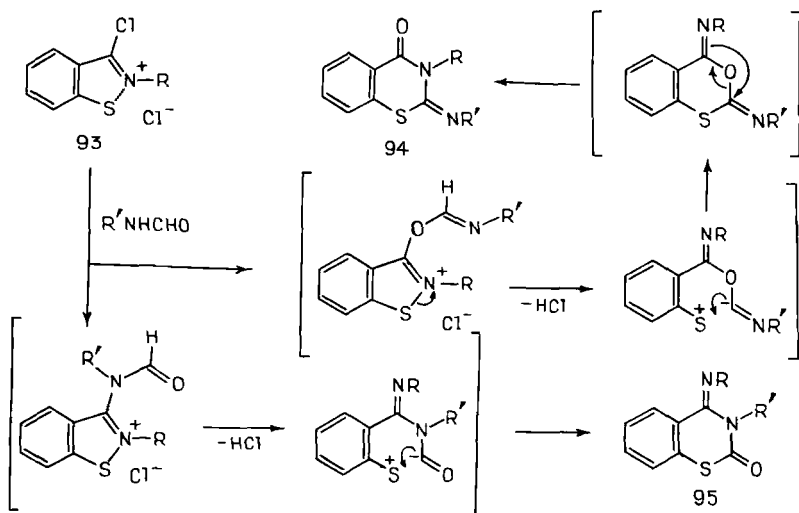
$\text{R}+\text{R}' = -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$

SCHEME 28



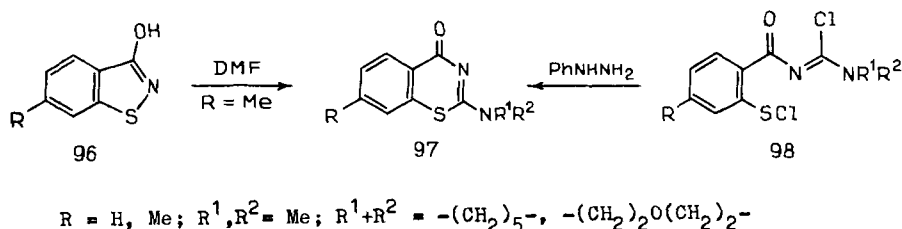
$\text{R} = \text{CONH}_2, \text{CN}, \text{COOMe}; \text{R}' = \text{H}, \text{Me}, \text{Ph}; \text{R}^2 = \text{H}, \text{Me}$

SCHEME 29



$\text{R} = \text{H}, \text{Alk}; \text{R}' = \text{Alk}, \text{Ph}$

SCHEME 30



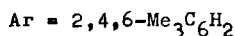
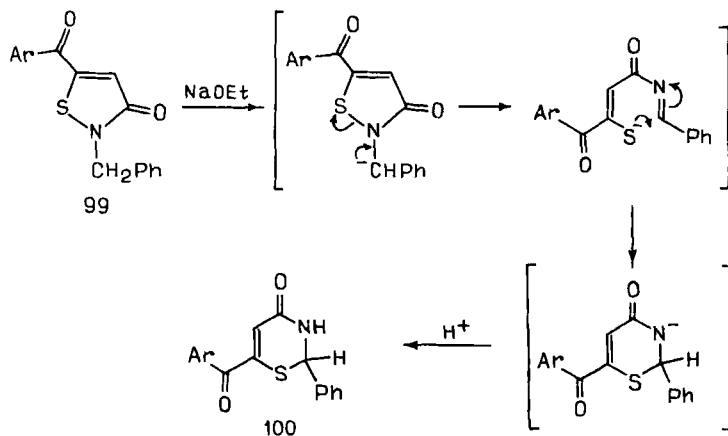
SCHEME 31

ment of 5-mesityloylisothiazolone **99** due to the elimination of a proton from the *N*-benzyl group, followed by a ring enlargement through the cleavage of isothiazolone S—N bond, affords 2,3-dihydro-TA **100** (85JHC1635) (Scheme 32).

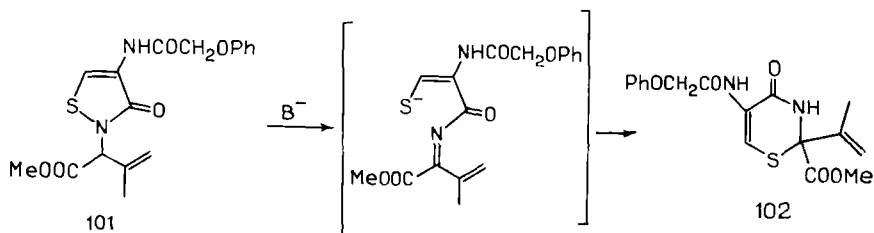
The same mechanism is realized in the case of 4-acylaminoisothiazolone **101** and results in the formation of 2,3-dihydro-TA **102** (73TL2159) (Scheme 33).

An interesting reaction between isothiazolone **103** and diazomalonester was described. It is assumed that the electrophilic carbene formed from a diazo compound attacks the sulfur atom to give ylide **104**. Its rearrangement affords product **105** [83JCS(CC)643] (Scheme 34).

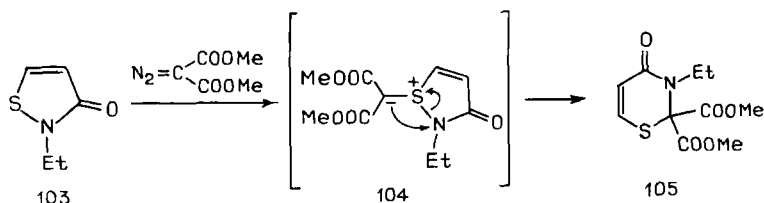
Other 2,3-dihydro derivatives have been obtained by the reduction of a C=N bond of nonreduced TAs; these derivatives are described in Section III,C,6.



SCHEME 32



SCHEME 33



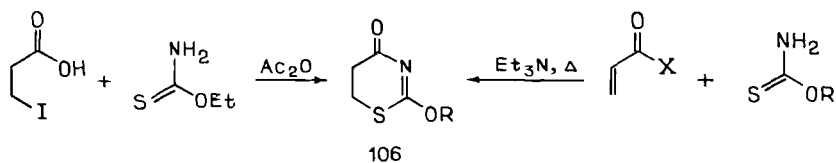
SCHEME 34

## 2. 5,6-Dihydro-1,3-thiazin-4-ones

2-Alkoxy- or 2-aryloxy-5,6-dihydro-TAs **106** may be obtained in two ways—from 3-iodopropionic acid (1891CB3848) and from acryloyl halides (89USP4839356—by the action of a thiocarbamate (Scheme 35).

2-Chloro-2,3-dihydro-TAs **109** were obtained by the conversion of 3-thiocyanopropionic acids **107** into chloroanhydrides **108** and subsequent cyclization (72GEP2010558) (Scheme 36).

2,3-Dihydro-TAs **111–114**, which are fused with other reduced rings, were synthesized by a [2 + 4]-cycloaddition reaction between thiobenzoyli-

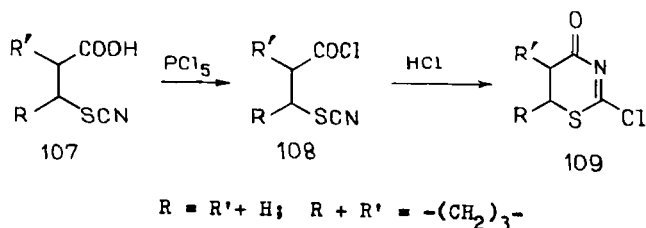


R = Ph, 1- and 2-ClC<sub>6</sub>H<sub>4</sub>, 1- and 2-MeC<sub>6</sub>H<sub>4</sub>, 1- and 2-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>;

X = Cl, Br

SCHEME 35



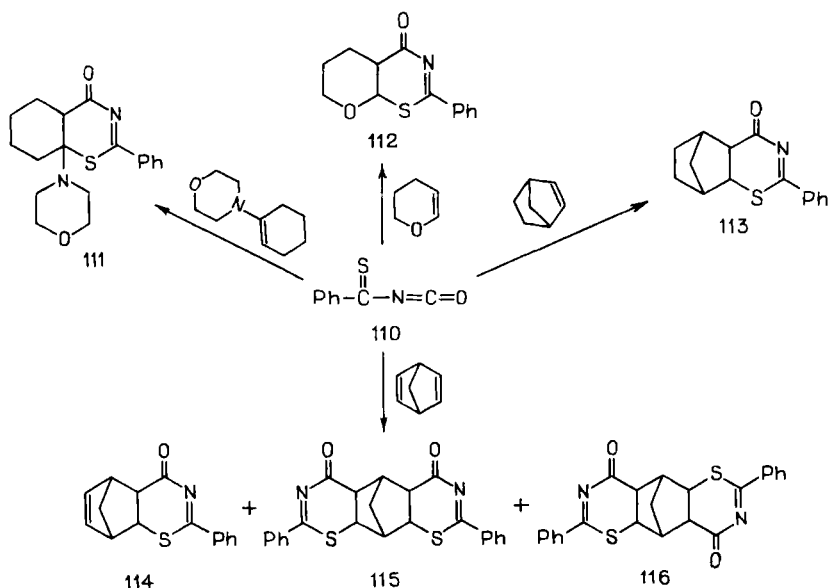


SCHEME 36

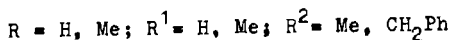
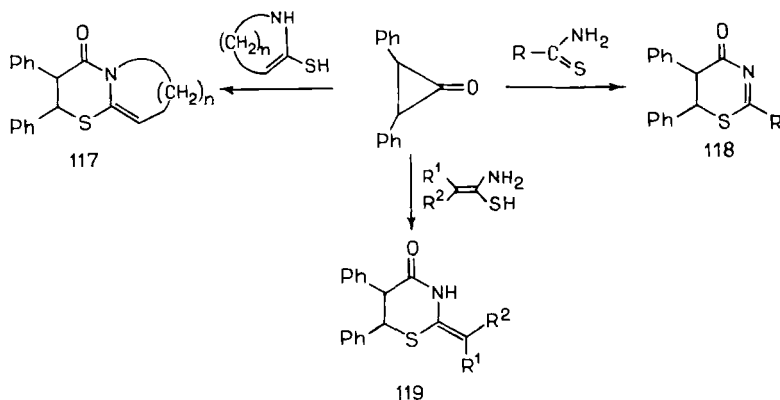
socyanate **110** and cyclic olefins such as 1-morpholinocyclohexene and dihydropyran (65CB3831), and norbornene and norbornadiene (67CB685) (Scheme 37). The last reaction affords a mixture of monoadduct **114** and two regioisomeric bis adducts **115** and **116**.

Different 5,6-diphenyl-5,6-dihydro-TAs **117–119** were synthesized by the ring enlargement of 2,3-diphenylcyclopropanone (71LA136) (Scheme 38).

*2-Imino or 2-amino Derivatives.* Much interest has attached to the syntheses of 2-imino- or 2-amino-5,6-dihydro-TAs owing to their high biological activity. The most widely used method is based on the interaction of thiourea or its *N*-substituted derivatives with 3-halogenopropionic acids (1885M821; 14CB159; 63ZOB3149; 64UKZ941; 67KGS1053) and 3-bromo-



SCHEME 37

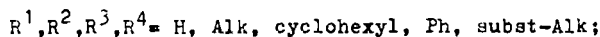
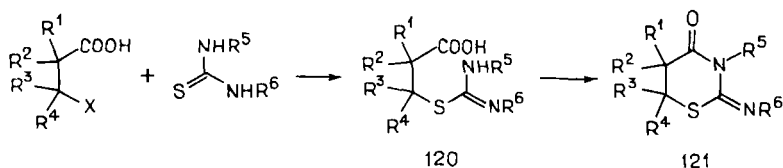


SCHEME 38

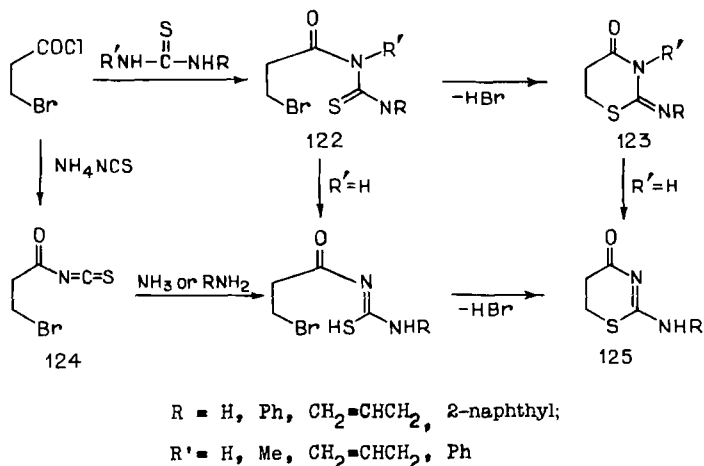
substituted aliphatic acids (52USP2585064; 55USP2679500; 62CPB19). The first step of this reaction is *S*-alkylation of the thiourea and formation of acids **120**. Their further cyclization under the action of oleum, acetic anhydride, or boiling acetic acid affords 2-imino-TAs **121**. In some cases, the reaction may proceed without the isolation of intermediates **120** (52USP2585064; 55USP2679500) (Scheme 39).

When the mixture of acetic anhydride and pyridine is used for the cyclization of acids **120** ( $R^5 = R^6 = H$ ), acetylation of the imino group takes place (58JOC897).

In the syntheses of 2-imino-5,6-dihydro- TAs **123** (**125**), 3-halogenopropionic acids are replaced by their chloroanhydrides. In this case, the first step of the reaction is *N*-acylation of thioureas accompanied by the formation of intermediates **122** (66UKZ610). These compounds may also be



SCHEME 39



SCHEME 40

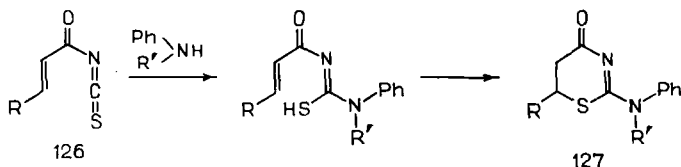
prepared and isolated in a different way—through acylisothiocyanate **124** (Scheme 40).

Isothiocyanates of acrylic acids **126** were also converted into TAs **127** in reactions with primary and secondary amines (80CCC2958) (Scheme 41).

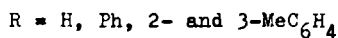
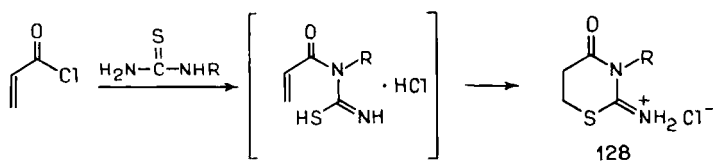
A number of methods of 2-imino-TA synthesis are based on the cyclization of acylthioureas containing an  $\alpha,\beta$ -unsaturated acid fragment. In the case of reactions of acryloyl chloride with thiourea (72MI1) or with *N*-substituted thioureas (73MI2), no *N*-acryloylthioureas were isolated and hydrochlorides of 3-substituted 5,6-dihydro-TAs **128** were obtained (Scheme 42).

For the syntheses of 2-imino-5,6-dihydro-TAs **129** with a substituent on the exocyclic N atom, the thermal cyclization of methacryloyl thioureas was used (67ZOR1468) (Scheme 43).

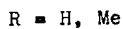
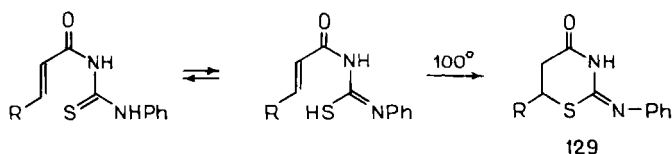
The bromination of vinyl acetic acid derivatives **130** affords products **131** or hydrobromide **132** (if  $R = H$ ). Subsequent debromination of **131** or **132**



SCHEME 41



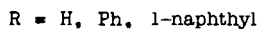
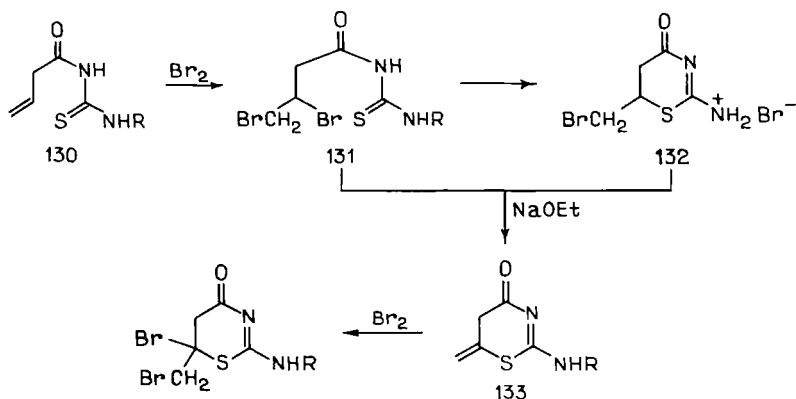
SCHEME 42



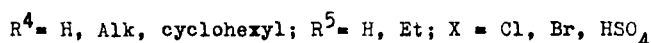
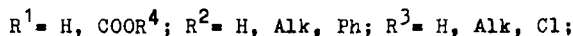
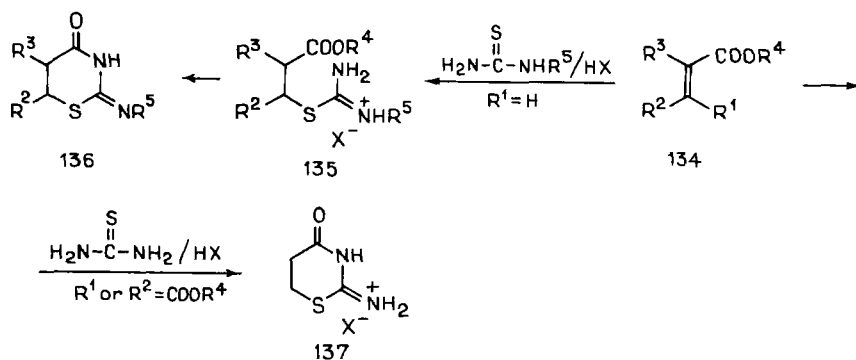
SCHEME 43

gives 6-methylene-TAs **133**. Bromination of **133** involves addition to the C=C bond (69UKZ526) (Scheme 44).

The general method of synthesis of 3-unsubstituted 2-imino-5,6-dihydro-TAs **136** and **137**, which is based on the reaction of  $\alpha,\beta$ -unsaturated carbon



SCHEME 44



SCHEME 45

acid esters **134** with thioureas, includes the isolation and subsequent cyclization of hydrochlorides or sulfates **135** by the action of aqueous ammonia or sodium acetate (58JOC1779). In the case of maleic or fumaric acids, hydrochlorides of 2-imino-TA **137** were obtained in one-pot syntheses (62AG906; 65GEP1187621) (Scheme 45).

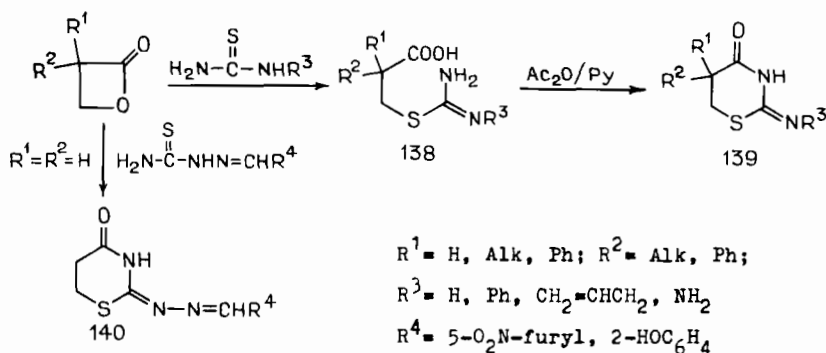
For the syntheses of 6-unsubstituted imines **139**, the reaction of  $\beta$ -propiolactone (48JA1001; 52USP2563034; 58JOC897) and its  $\alpha$ -substituted derivatives (66BRP1007587) with thioureas was investigated. At the first step, acids **138** were isolated. The cyclization of **138** in acetic anhydride or in its mixture with pyridine results in TAs **139**. Thiosemicarbazones react in an analogous way to give TAs **140** in one pot (62JOC188; 71JAP71/22151) (Scheme 46).

3-Phenyl-substituted imine **142** was obtained by reaction of acylthiourea **141** with potassium thiocyanate. The reaction proceeds via an unusual thiocyanic acid elimination (69PHA96) (Scheme 47).

### 3. 2,3,5,6-Tetrahydro-1,3-thiazin-4-ones

2,3,5,6-Tetrahydro-TAs are of great interest because of their high—and highly variable—biological activity. Three methods have been used for their synthesis.

The first consists in the reaction of 3-mercaptopropionic acid with azomethines (method A), in which it is not necessary to isolate the Schiff



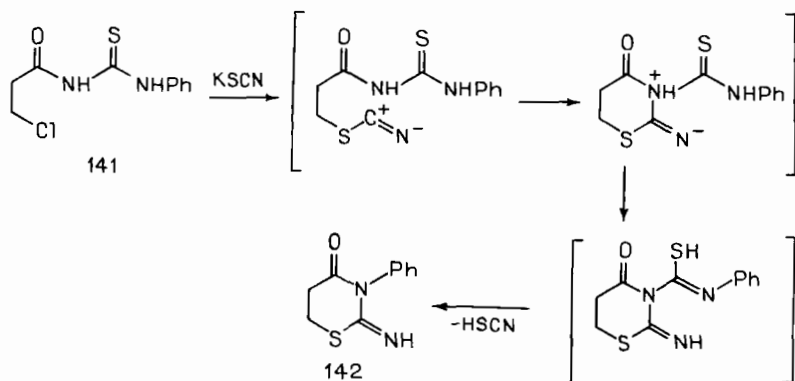
SCHEME 46

bases. For the syntheses of 2- and 3-unsubstituted compounds, paraformaldehyde and ammonium carbonate are used, respectively (Scheme 48).

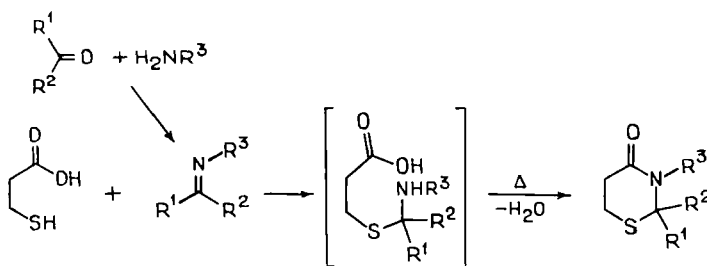
The second method consists in the reaction of 3-mercaptopropionic acid amides with various aldehydes and ketones (method B); this reaction proceeds via the formation of thiohemiacetal **143**. Method B was modified (in the case of *p*-chlorobenzaldehyde) by means of dithioacetal **144**, which was isolated and then introduced into the reaction with the second mole of aldehyde (Scheme 49).

The third method involves the oxidative cyclization of *S*-benzylpropionic acid amides **145** by acetyl peroxide (method C) to afford tetrahydro-TAS **146** (Scheme 50).

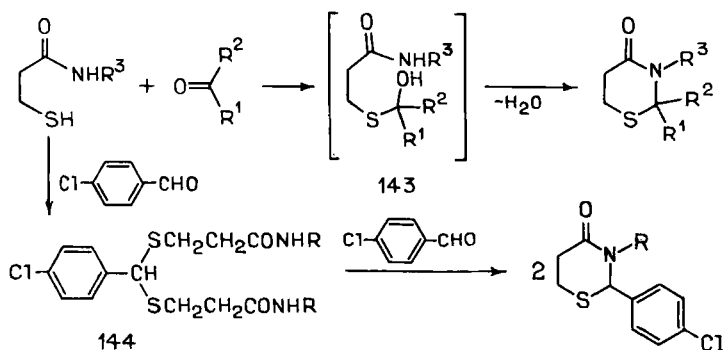
Information about these compounds—their methods of synthesis (A, B or C), biological activity, and references—is given in Table I.



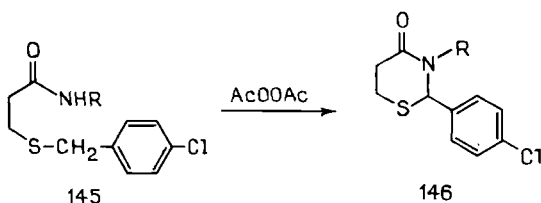
SCHEME 47



SCHEME 48



SCHEME 49

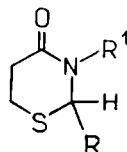


SCHEME 50

#### 4. 2,3-Dihydro-1,3-benzothiazin-4-ones

The most frequently used method of synthesis of 2,3-dihydro-1,3-benzo-TAs **150** is the reaction of 2-mercaptobenzamides with carbonyl compounds—paraformaldehyde (53AP330), and aliphatic (61AP556; 62-BSF502) and aromatic (61AP556; 64JOC2068; 74JAP73/31114; 78T1031)

TABLE I  
2,3,5,6-Tetrahydro-1,3-thiazin-4-ones

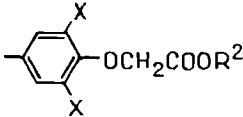
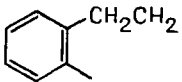


R	R¹	Method of synthesis	Biological activity	Reference
Ph; 2-, 3-, and 4-pyridyl; 2-thienyl	H, Me, Et, Pr, PhCH₂, PhCH₂CH₂	A	CNS depressant	58JA3469
4-BrC₆H₄; 4-ClC₆H₄; 4-MeOC₆H₄	H, Me, Et	A	CNS depressant; anticonvulsant; antipyretic	59BRP815203
Alkoxyphenyl	H	A	gastric ulceration inhibitor	82EUP50003
H, chloro-, and dichlorophenyl	Et, (CH₂)₂OMe, (CH₂)₂OEt, (CH₂)₃OMe, (CH₂)₂OPh	A	CNS depressant; anticonvulsant	62BRP866761 63USP3082209; 63USP3093639
H	—(CH₂) <sub>n</sub> —H ( <i>n</i> = 2, 4, 6, 7), —(CH₂)₂OMe	A	anticonvulsant	65USP3155655

(continued)



TABLE I  
(Continued)

R	R <sup>1</sup>	Method of synthesis	Biological activity	Reference
2-, 3-, 4-FC <sub>6</sub> H <sub>4</sub> ; 2,6-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Me	A	antielectrical and -chemical shock; paralyzing agent hypothermic agent	70JHC955
Ph; 2-ClC <sub>6</sub> H <sub>4</sub> ; 4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	2-, 3-, and 4-pyridyl	A	—	64AC(R)607
4-ClC <sub>6</sub> H <sub>4</sub>	Me	B	tranquilizer	71JAP70/26495
4-ClC <sub>6</sub> H <sub>4</sub>	H; —(CH <sub>2</sub> ) <sub>n</sub> —H (n = 1, 2, 3, 4); PhCH <sub>2</sub>	C	tranquilizer; muscle relaxant	75JAP74/116079
(CH <sub>2</sub> ) <sub>n</sub> COOR <sup>2</sup> (R <sup>2</sup> = H, Me, Et; n = O-5)	H, Me			74JAP74/35389; 76JAP75/149689
 (X = H, Br; R <sup>2</sup> = H, Et)	H	B	antitubercular activity	78T1031
4-NC(CH <sub>2</sub> ) <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ; (CH <sub>2</sub> ) <sub>5</sub> CONH-cyclohexyl	H	A	antibacterial agent; trichonemicidal agent	70FRP1552211
R + R <sup>1</sup> = 				

aldehydes and ketones. The reaction with *N*-substituted piperidin-4-ones has also been described (74JAP73/31114).

Dithiosalicylamide **147** may also be used if an excess of benzaldehyde is employed for the reduction of the S—S bond (47JCS763).

In addition, other compounds have been used instead of aldehydes or ketones. Reactions with benzal chloride (55BSF1518) and ethyl orthoformate (73JHC149) result in compounds **148** and **149**, respectively.

Reaction between 2-mercaptobenzamides and acetylenic esters gives vinyl sulfides **151** at the first stage. Their cyclization affords 2,3-dihydrobenzo-TAs **152**, which contain carbomethoxy groups.

2,3-Dihydrobenzo-TAs of this type may be obtained from 2-mercaptobenzoic acid and its esters. The reaction with dimethyl-acetylenedicarboxylate affords acid **153**, which is converted into a chloroanhydride. Further cyclization by the action of ammonia gives compound **152** ( $R^3 = H$ ) (67JOC2678; 70JHC1007). *N*-Hydroxy- (57USP2776281) and *N*-amino-2,3-dihydro-1,3-benzothiazin-4-ones [73DIS(B)3561] were obtained from 2-mercaptobenzohydroxamic acid and 2-mercaptobenzhydrazide, respectively (Scheme 51).

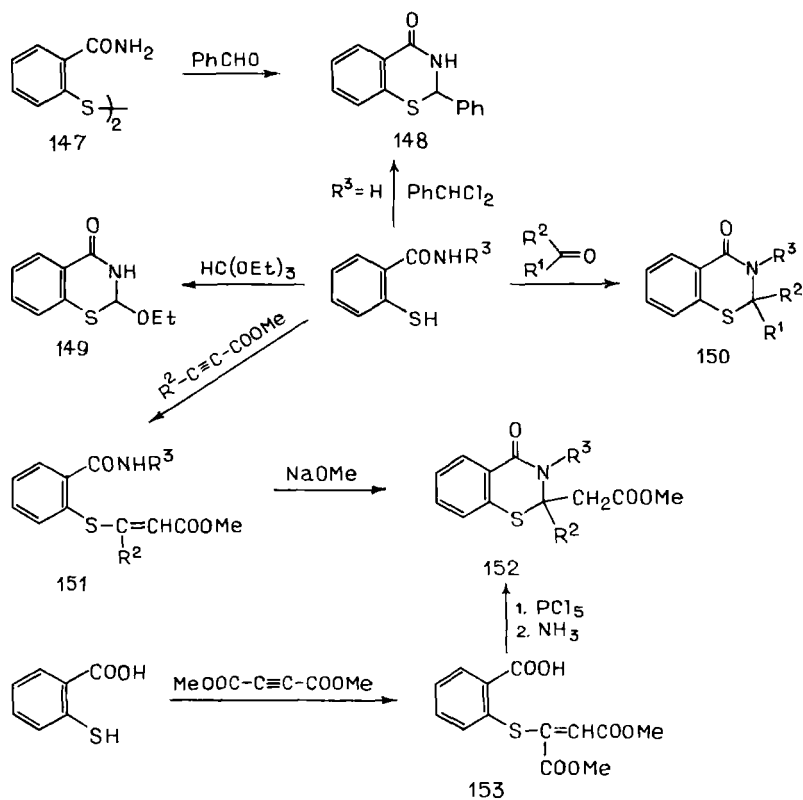
2,3-Dihydrobenzo-TAs **154** and **155**, which possess high biological activity, were synthesized by condensing 2-mercaptobenzoic acid and its esters with *N*-acylhydrazones of aromatic aldehydes (70MI1) and Schiff bases obtained from functionally substituted amines [64AC(R)607; 69-USP3455915, 69USP3459748; 72FRP2043464]. Compounds **155** may also be obtained in one pot from 2-mercaptobenzoic acid, aromatic aldehydes, and primary amines (63JOC2160) (Scheme 52).

*N*-Substituted 2,3-dihydrobenzo-TAs **157** were obtained by cyclization of benzyl-(*o*-carbamoyl)phenyl sulfoxides **156**. However, this reaction is not characteristic of other sulfoxides **156** (when  $R \neq Ph$  and  $R = H$ ), which afford either 2-acetyl-1,2-benzisothiazol-3-one **158** or 1,3-benzothioxan-4-ones **159** (74T2641) (Scheme 53).

2-Benzoyl-2,3-dihydrobenzo-TA **161** was synthesized by recyclization of *N*-phenacylbenzothiazol-3-one **160** under the action of triethylamine (76JOC1325) (Scheme 54).

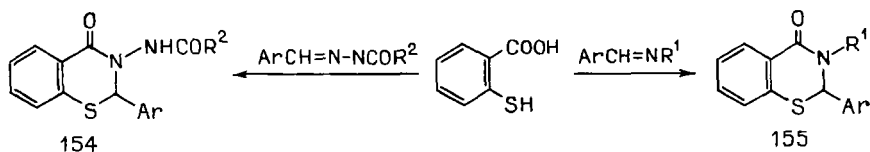
Another type of recyclization is realized for *N*-acylbenzothiazol-3-ones **162** by means of their reduction. But this rearrangement takes place only when  $R = \text{alkyl}$  (47JCS763), in which case the result is 2,3-dihydrobenzo-TA **163** (Scheme 55).

2,3-Dihydrobenzo-TAs **164** may be obtained from compounds containing a 1,3-thiazine ring, for example, by oxidation of 2,3-dihydro-1,3-benzothiazine-4-thiones (55BSF1518) (Scheme 56). The reduction of 1,3-benzo-TA, affording 2,3-dihydro derivatives, is described in Section III,C,6.



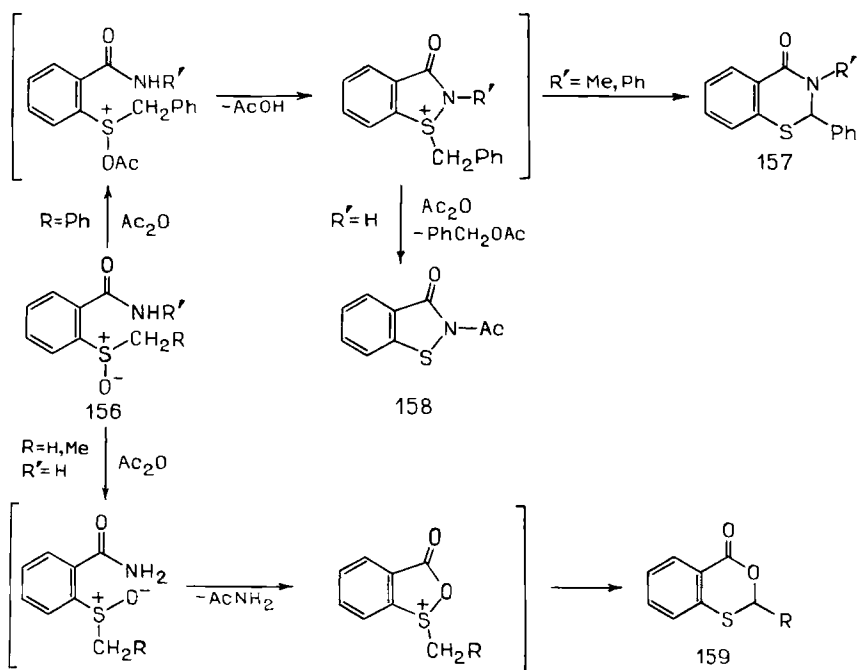
$\text{R}^1 = \text{H}, \text{Me}; \text{R}^2 = \text{Me}, \text{Et}, \text{Ar}, \text{CH}_2\text{COOAlk}, -(\text{CH}_2)_5\text{COOAlk},$   
 $-\text{C}_6\text{H}_4\text{OCH}_2\text{COOAlk-p}; \text{R}^1+\text{R}^2 = -(\text{CH}_2)_5-, -(\text{CH}_2)_2\text{NAlk}(\text{CH}_2)_2-;$   
 $\text{R}^3 = \text{H}, \text{Alk}, \text{OH}, \text{NH}_2$

SCHEME 51

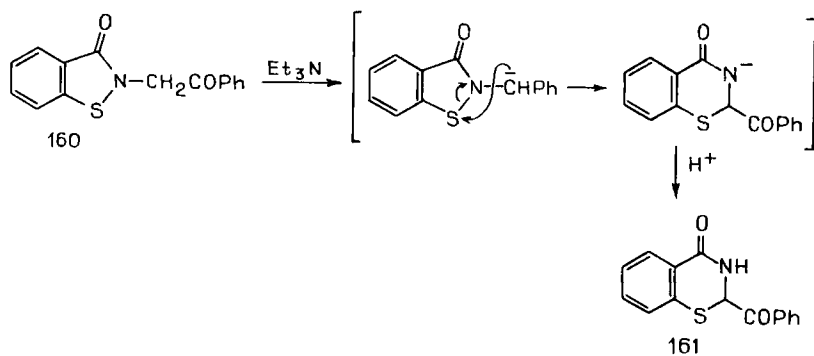


$\text{R} = \text{H}, \text{Alk}; \text{R}^1 = \text{Alk}, -(\text{CH}_2)_3\text{OH}, -(\text{CH}_2)_3\text{Cl}, -(\text{CH}_2)_3\text{NMe}_2, \text{NAlk}_2;$   
 $\text{R}^2 = \text{Ar}, 4\text{-pyridyl}$

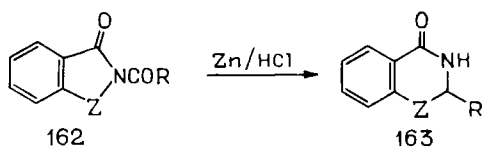
SCHEME 52



SCHEME 53

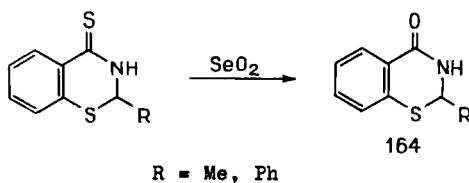


SCHEME 54



$R = \text{Alk, PhCH}_2$ ;  $Z = \text{S, S}^+-\text{O}^-$

SCHEME 55



SCHEME 56

### D. 1,3-THIAZIN-4-ONES CONDENSED WITH HETEROCYCLES

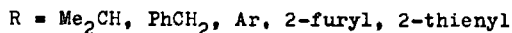
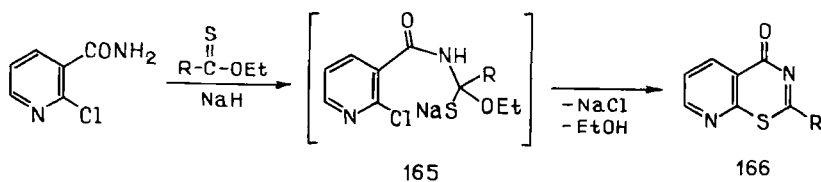
Recently, interest in the syntheses of polyheterocyclic systems containing fused 1,3-thiazin-4-ones has been growing due to the search of new biologically active substances. The synthetic methods used for obtaining these compounds are the same as those used for benzo-TAs.

#### 1. *e*-Fused Systems

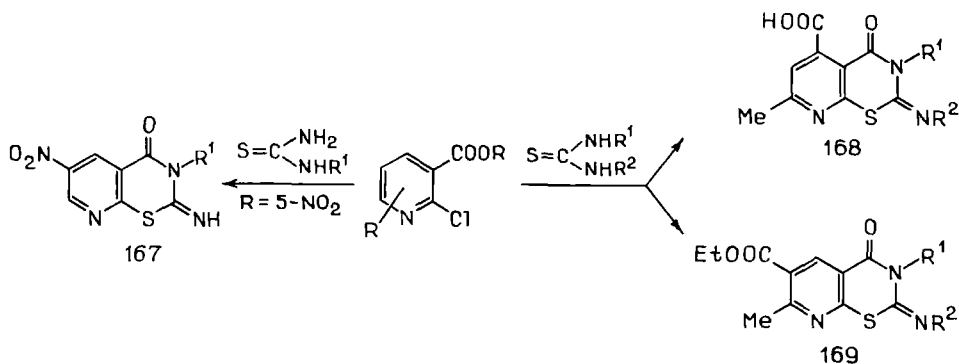
**4-Oxo-1,3-pyridothiazines.** Most work on TAs fused with heterocycles has been devoted to 4-oxo-1,3-pyridothiazines. A number of pyrido-TAs **166** were obtained from 2-chloronicotinamide and thioesters in the presence of sodium hydride (89T4153) (Scheme 57). The role of sodium hydride consists in eliminating a proton from the amide group; the resulting *N*-anion attacks the thiocarbonyl function, forming intermediates **165** whose cyclization gives pyrido-TAs **166**.

Frequently, the starting materials for the syntheses of 2-iminopyrido-TAs are 2-chloronicotinic acid derivatives—esters or isothiocyanates. The second reagent may be a substituted thiourea or it may be a primary or secondary amine. Imines **167** (73MI1), **168** (84POP122833), and **169** (86FES899) were prepared in this way (Scheme 58).

2-Aminopyrido-TAs **172** were obtained from isothiocyanates **170** and



SCHEME 57



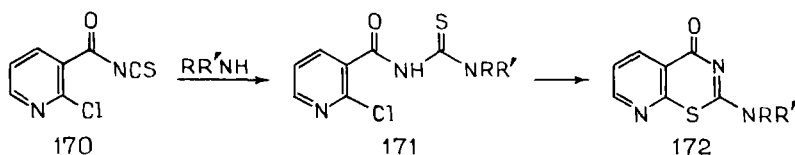
SCHEME 58

amines. Further cyclization in boiling ethanol of the intermediate thioureas **171** yields compounds **172**. The thioureas **171** were isolated as stable intermediates when primary amines were used. In the case of secondary amines, the final products **172** were isolated directly (83CCC3315) (Scheme 59).

2-Mercaptonicotinic acids **173** were used in the syntheses of imines **174** by reaction with carbodiimides (81MI1) (Scheme 60).

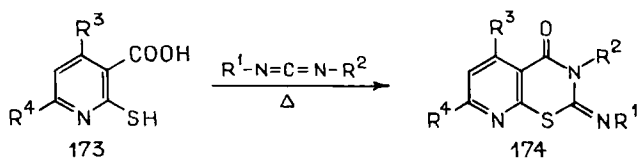
Mercaptoquinolinic acid **175** reacts with cyanoamide and with cyanothioureas to give imines **176** and **177**, respectively (73KGS644) (Scheme 61).

*4-Oxo-1,3-benzothienothiazines*. 2-Aminobenzothieno-TAs were obtained by the reaction of isothiocyanates **178** with primary (86CCC2839) and secondary (83S929) amines. The initially formed thioureas **179** and **180** were then transformed into TAs **181** and **182** by photocyclization. In the second stage, the reactivity of monosubstituted thioureas **179** is lower than that of disubstituted derivatives **180**, owing to the presence of a strong hydrogen bond. Consequently, the existence of compounds **179** in conformation A tends to inhibit the cyclization (Scheme 62).



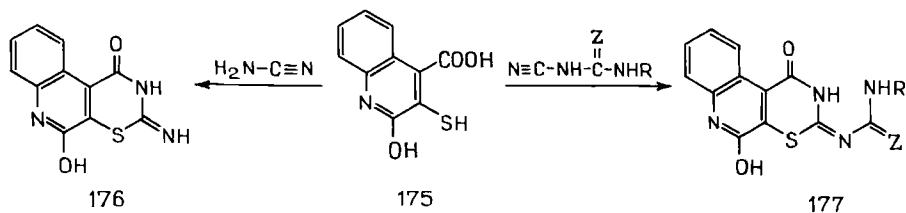
$\text{R} = \text{H}, \text{Ph}; \text{R}' = \text{H}, \text{Alk}, \text{PhCH}_2, \text{Ar}; \text{R} + \text{R}' = -(\text{CH}_2)_5-, -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$

SCHEME 59



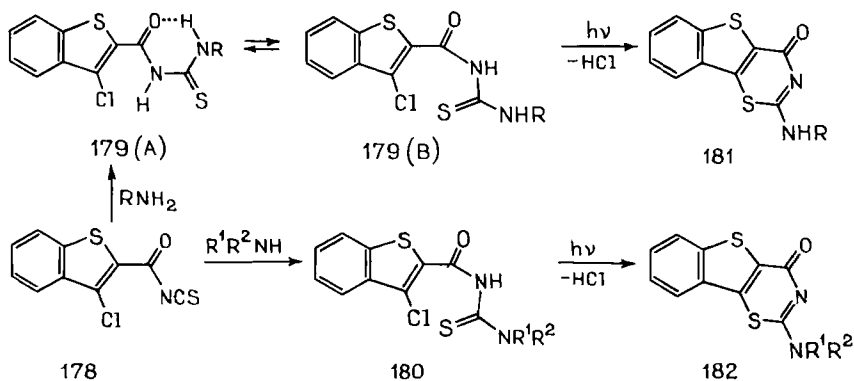
$\text{R}^1 = \text{H, Alk, cyclohexyl, CH}_2=\text{CHCH}_2$ ;  $\text{R}^2 = \text{H, Alk, COOMe, Br, 4-ClC}_6\text{H}_4$ ;  $\text{R}^3 = \text{H, Me}$ ;  $\text{R}^4 = \text{H, Me}$

SCHEME 60



$\text{R} = \text{H, Me, Ph, 2-naphthyl}$ ;  $\text{Z} = \text{O, S}$

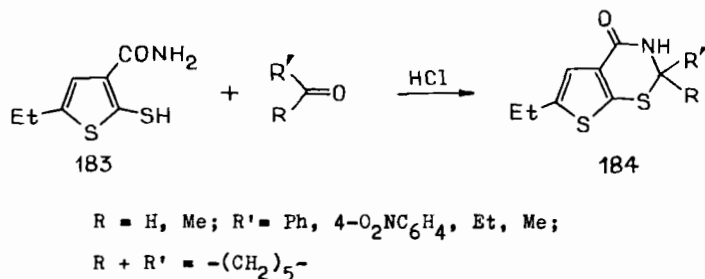
SCHEME 61



$\text{R} = \text{Et, PhCH}_2, \text{CH}_2=\text{CHCH}_2, \text{Ph}(\text{CH}_2)_2, \text{cyclohexyl}$ ;

$\text{R}^1 = \text{Alk, Ph}$ ;  $\text{R}^2 = \text{Alk, Ph}$ ;  $\text{R}^1 + \text{R}^2 = -(\text{CH}_2)_5-, -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$

SCHEME 62



SCHEME 63

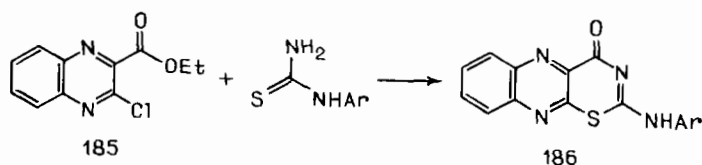
The synthesis of 2,3-dihydrothieno[3,2-*e*]-1,3-thiazin-4-ones **184**, in which the orientation of the thiophene ring toward the 1,3-thiazine ring is different, is based on a reaction between mercaptoamide **183** and various ketones (72KGS909) (Scheme 63).

*4-Oxo-1,3-quinoxalinothiazines.* 2-Arylaminoquinoxalino-TAs **186**, which act as central nervous system (CNS) depressants, were obtained by the reaction of the chlorocarboxylate **185** with various arylthioureas [93IJC(B)901] (Scheme 64).

## 2. *b*-Fused Systems

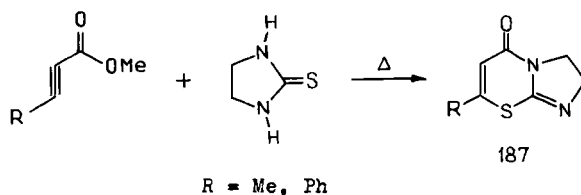
*4-Oxo-1,3-imidazothiazines.* A number of reactions have been used for the construction of imidazo[2,1-*b*]-1,3-thiazin-4-one. For example, reaction between acetylenic acid esters and imidazolinethione is the route to imidazolino-TAs **187** [68JCS(C)2510] (Scheme 65).

Some reduced derivatives of imidazo[2,1-*b*]-1,3-thiazin-4-one have been described. For example, the reaction of 2-mercaptobenzimidazole with acryloyl chlorides results in TAs **188** (91MI2). A similar iodine-containing compound ( $\text{R} = \text{H}$ ) was synthesized by the cyclization of acid **189** (92MI2) (Scheme 66).

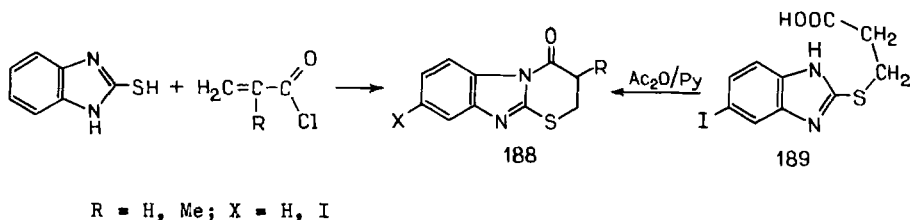


SCHEME 64





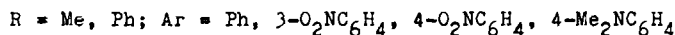
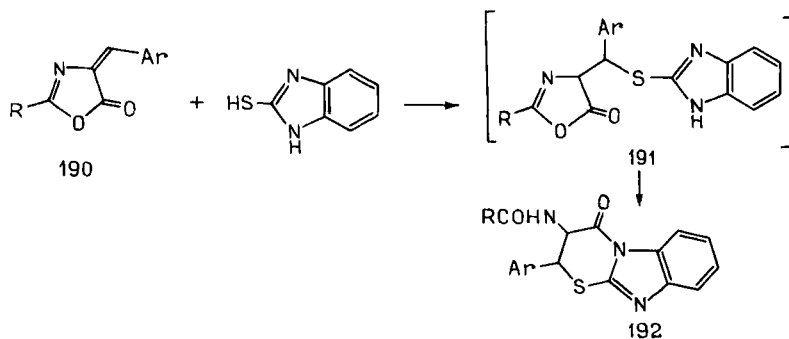
SCHEME 65



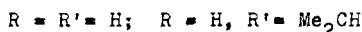
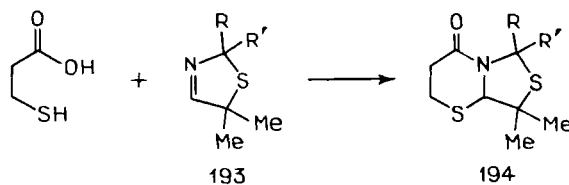
SCHEME 66

One-pot syntheses involving a ring transformation consist in Michael-type addition of 2-mercaptobenzimidazole to 4-benzylideneoxazol-5-ones **190** followed by recyclization of the adduct **191** to give acylamino derivatives of dihydrobenzimidazo-TA **192** (92MI3) (Scheme 67).

Fully reduced thiazolo-TAs **194** were obtained from 3-thiazolines **193** and 3-mercaptopropionic acid (92T10277) (Scheme 68).



SCHEME 67



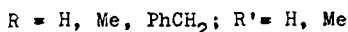
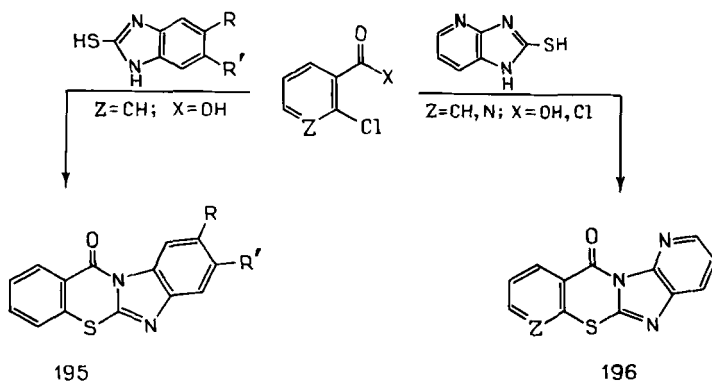
SCHEME 68

### 3. Simultaneously *b*- and *e*-Fused Systems

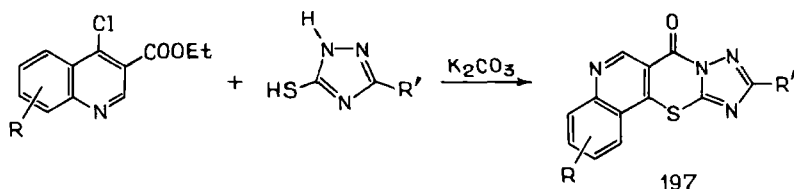
Reactions of 2-mercaptobenzimidazole and 2-mercapto-1*H*-imidazo[4,5-*b*]pyridine with 2-chlorobenzoic or 2-chloronicotinic acids lead to tetracyclic heterosystems **195** and **196**, respectively [88IJC(B)1142] (Scheme 69).

A similar reaction leading to the tetracyclic system **197** was described (90SC2473) (Scheme 70).

Another approach to the synthesis of simultaneously *b*- and *e*-fused heterosystems containing 1,3-thiazin-4-one fragments is based on the use of a thiazinone ring prepared in advance. Thus, 2-imino-3-amino-TA **79**, obtained from hydrazide **198**, was applied to the syntheses of triazolobenzo-TAs **199**, **200**, and **201** (75M11). Amine **201** may be obtained from hydrazide



SCHEME 69



R = H, 8- and 9-Alk, OMe, Cl, F, NO<sub>2</sub>, 10-Alk;

R' = H, Alk

SCHEME 70

**198** and an excess of cyanogen bromide in one pot (83JHC1215) (Scheme 71).

Under Mannich-reaction conditions, pyrido-TA**202** was converted into thiazinones **203** fused with triazine and pyridine rings (85FES65) (Scheme 72).

The tetrazolobenzo-TA **204** was obtained by a reaction of 2-chloro-1,3-benzothiazin-4-one with sodium or dibutylammonium azide (70CB413) (Scheme 73).

### III. Reactivity

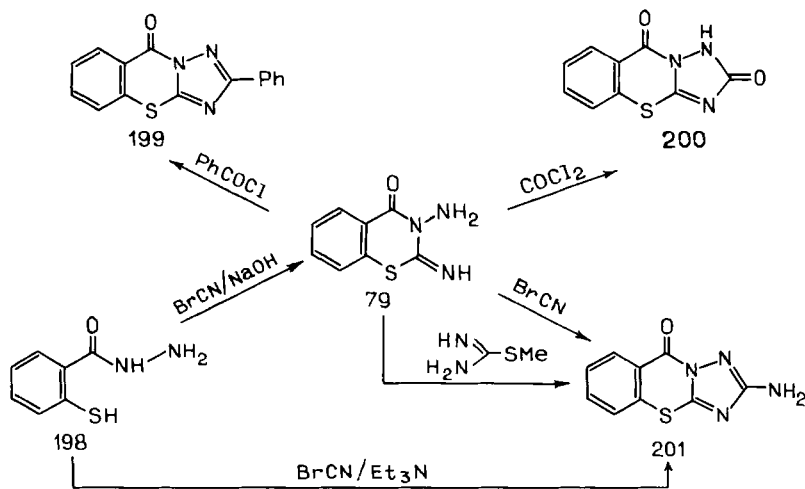
#### A. GENERAL SURVEY

The reactivity of TAs may be considered in two ways. The first consists in describing all the reactions of each separate class of compounds. This was done in early reviews (79KGS291; 86KGS3). The second approach—that of the present review—is based on the classification into types of reactions of different compounds. The latter approach allows one to focus on general and specific peculiarities of transformations and to compare the chemical behavior of various groups of TA derivatives.

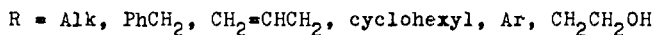
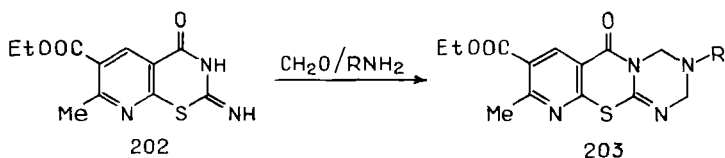
#### B. REACTIVITY OF THE RING ATOMS WITH ELECTROPHILES

##### 1. Protonation

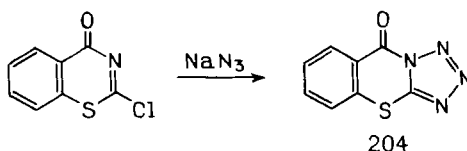
*A priori*, TA may be protonated at three positions—at the S or N atoms or at the C=O group. One group of authors postulated the formation of



SCHEME 71

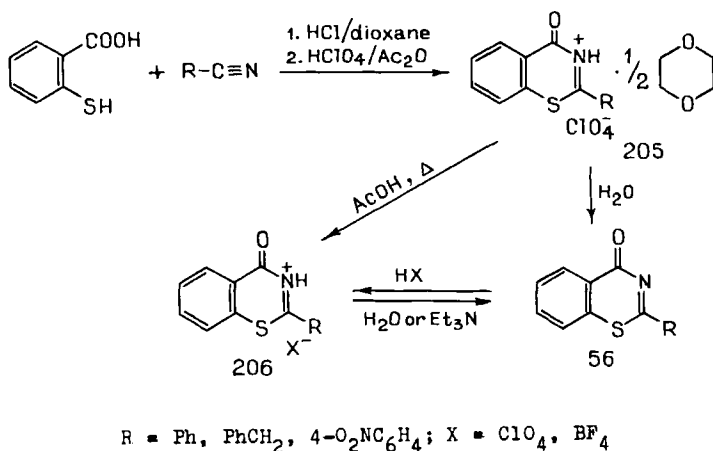


SCHEME 72



SCHEME 73

*O*-protonated 3-azathiopyrylium forms **38** (Scheme 8). On the basis of <sup>1</sup>H NMR spectra it was assumed that 2-cyanomethyl-1,3-benzothiazin-4-one exists in one of its three protonated forms (84H1677). In several papers (53AP437; 57MI1; 60MI1), the formation of crystalline hydrochlorides of 1,3-benzo-TA was mentioned; these compounds proved to be unstable,



SCHEME 74

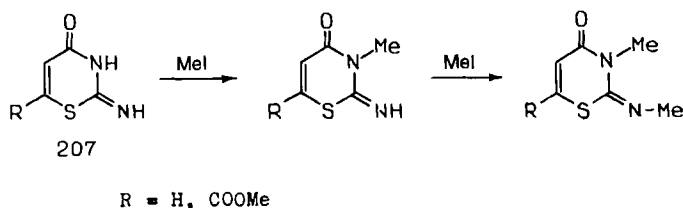
deprotonating in open air. In such cases, no position of protonation could be determined because of the product lability.

The first stable perchlorates of 1,3-benzo-TA were isolated as dioxane complexes **205** in a reaction between 2-mercaptobenzoic acid and nitriles in the presence of 70%  $\text{HClO}_4$  and acetic anhydride. Heating these complexes in acetic acid affords salts **206**, which may be transformed into benzo-TA **56**. Protonation of **56** initially gives cations **206**, whose IR spectra show that they exist in an NH form (there is a strong bond at  $1700\text{--}1730\text{ cm}^{-1}$ ) (85KGS562) (Scheme 74).

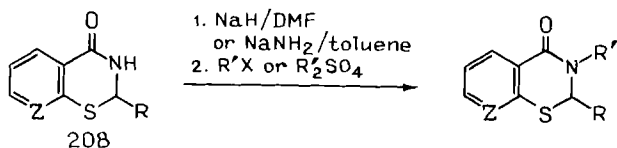
## 2. Alkylation

Alkylation of monocyclic TA was investigated in the case of 2-imino-TA **207**. The reaction goes first at the endocyclic N-3 atom and then at the imino group (67CB3671) (Scheme 75).

2,3-Dihydrobenzo- and pyrido-TAs **208** were alkylated at the N-3 position by alkyl iodides (for  $\text{Z} = \text{CH}$ ) or bromides (for  $\text{Z} = \text{N}$ ) in the presence



SCHEME 75



for Z = CH    R' = Me, Et; X = I; R = Alk, Ar

for Z = N    R' = CH<sub>2</sub>=CHCH<sub>2</sub>, PhCOCH<sub>2</sub>, Me<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>-, Ar; X = Br;  
R = Ar

SCHEME 76

of NaH in DMF (89T4153). In the case of benzo derivatives (Z = CH), NaNH<sub>2</sub> in toluene and dialkyl sulfates were also used (62BSF502) (Scheme 76).

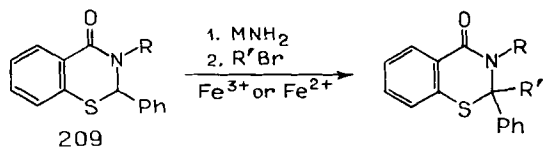
For the introduction of an alkylamino group into the 2 position of *N*-substituted compounds **209**, amides of alkaline metals in liquid ammonia were used as generators of C-2 anions (70USP3475423; 71GEP1926071; 72BRP1275593, 72FRP2047871) (Scheme 77).

### 3. Mannich Reaction

2-Iminopyrido[3,2-*e*]-TAs **210** react with formaldehyde and cyclic secondary amines at the N-3 atom of the thiazine ring to give 3-aminomethyl derivatives **211** (85FES58) (Scheme 78).

### 4. Acylation

Unlike alkylation, the acylation of 2-imino-TA **207** goes at the exocyclic imino group to give products **212**, which exist in imino and amino forms (67CB3671) (Scheme 79).

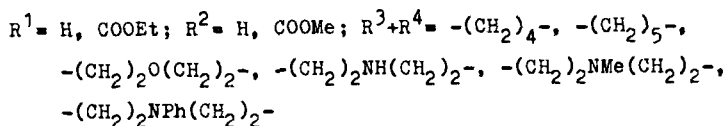
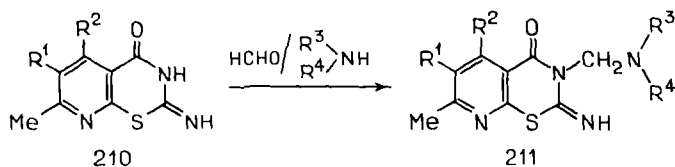


R = Alk; R' = Me<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>-, Et<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>-, Me<sub>2</sub>N(CH<sub>2</sub>)<sub>3</sub>-,

HO(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>-

M = Na, K

SCHEME 77

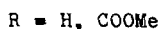
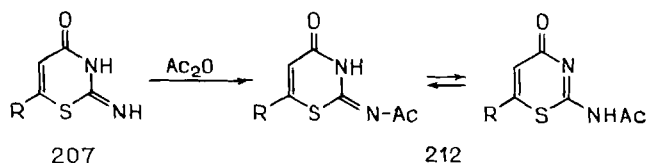


SCHEME 78

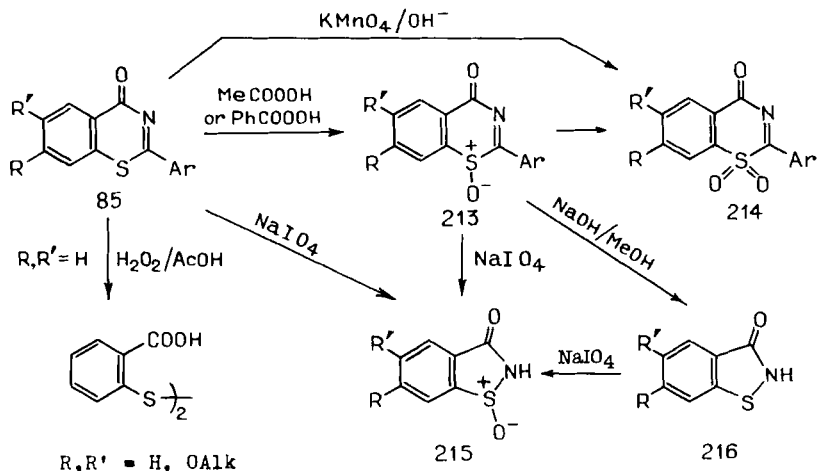
### 5. Oxidation

Oxidation has been studied more completely for benzo-TAs. The structure of the products depends on the nature of the oxidizer and the reaction conditions, 2-Arylbenzo-TAs **85** were oxidized by potassium permanganate into sulfones **214** (69BSF2524). The use of peracetic or perbenzoic acids makes it possible to obtain first sulfoxides **213**, then sulfones **214** (89MI1). The action of 30% hydrogen peroxide in acetic acid leads to ring cleavage and the formation of dithiosalicylic acid and arylamides (57MI1). The reaction of benzo-TAs **85** and their sulfoxides **213** with sodium periodate results in ring contraction and gives *S*-oxides of benzoisothiazoles **215**. The recyclization of sulfoxides **213** takes place in their reaction with NaOH; in this case, however, the products are benzoisothiazoles **216**. Their oxidation by sodium periodate affords sulfoxides **215** (89MI1) (Scheme 80).

2,3-Dihydrobenzo-TAs **150** also give various products of oxidation, depending on the substituents and on the kind of oxidizing agents. 3-Unsubstituted benzo-TAs may react in three ways: under the action of *m*-chloroperbenzoic acid, 2,2-dimethyl-2,3-dihydrobenzo-TA gives sulfoxide **217** (70JCS335); the action of hydrogen peroxide in acetic acid leads to 2-sulfobenzoic acid; and the oxidation of 2-methyl-2,3-dihydrobenzo-TA by

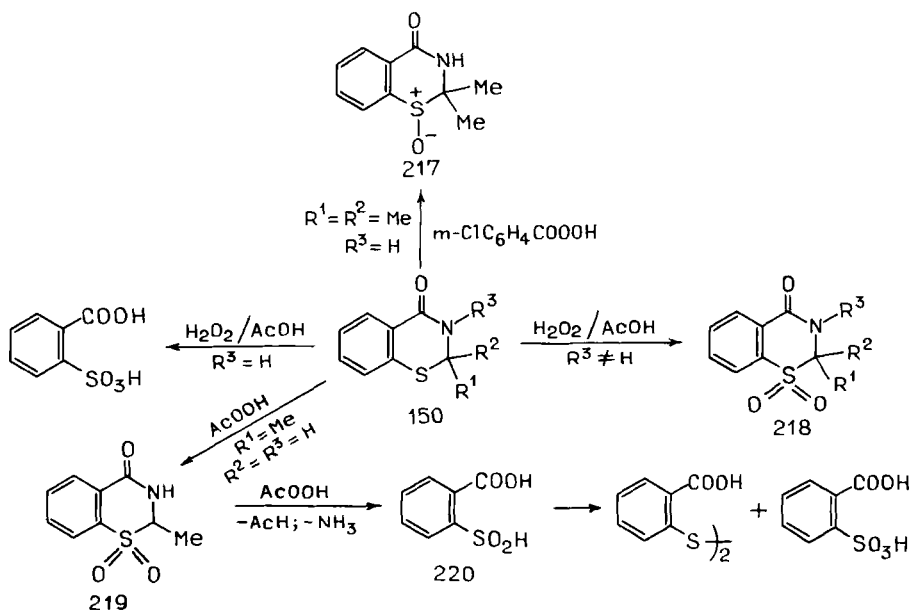


SCHEME 79



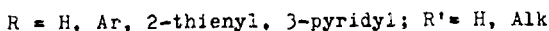
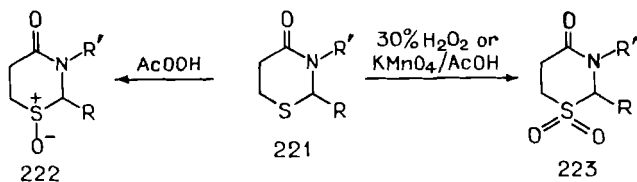
SCHEME 80

peracetic acid results in sulfone **219**, which is oxidized into sulfinic acid **220**. The disproportionation of this acid gives a mixture of dithiosalicyclic and 2-sulfobenzoic acids. *N*-Substituted 2,3-dihydrobenzo-TAs react with hydrogen peroxide to give only sulfones **218** (53AP330) (Scheme 81).



SCHEME 81





SCHEME 82

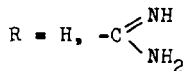
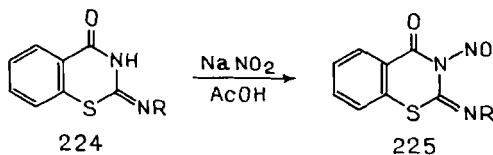
In the case of 2,3-disubstituted dihydrobenzo-TAs, oxidation by potassium permanganate results in a mixture of sulfoxides and sulfones (69USP3455915). Only sulfones were obtained by potassium permanganate oxidation (63JOC2160; 70JHC1007).

The oxidation of monocyclic 2,3,5,6-tetrahydro-TAs has been thoroughly studied, because many biologically active substances have been found among the reaction products, including such well-known drugs as chloromesanone and dichloromesanone, which are used as analgesics and muscle relaxants.

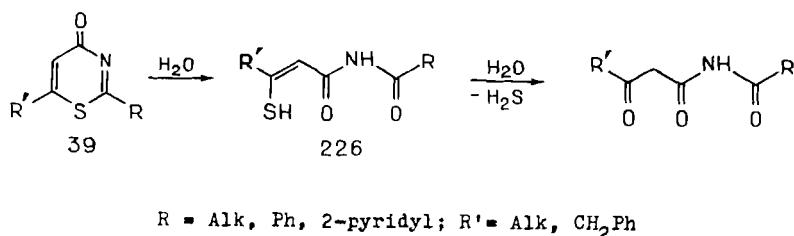
Oxidation of TAs **221** by 40% peracetic acid makes it possible to obtain sulfoxides **222** (62BRP866761; 63USP3082209, 63USP3093639; 65USP-3155655). Syntheses of sulfones **223** have been carried out by two methods—the action of potassium permanganate in acetic acid (58JA3469; 59BRP815203; 63USP3082209, 63USP3093639; 65USP3155655; 70JHC955) and the action of 30% hydrogen peroxide in the presence of a sodium tungstate catalyst (76JAP75/149689) (Scheme 82).

## 6. Nitrosation

Only one nitrosation of imines **224** has been described; it gives *N*-nitroso derivatives **225** (63ZOB213) (Scheme 83).



SCHEME 83



SCHEME 84

### C. REACTIVITY OF THE RING ATOMS WITH NUCLEOPHILES

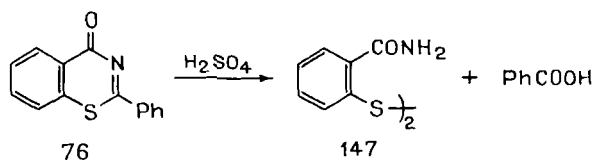
#### 1. Hydrolysis

Thiazinones **39** undergo ring opening under very mild conditions (aqueous acetone,  $25^\circ\text{C}$ ) to give *N*-acylamides of 3-mercaptoacrylic acid **226**. But these compounds are unstable and afford *N*-acylamides of 3-oxoacids if not quickly isolated from the reaction mixture (81H851) (Scheme 84).

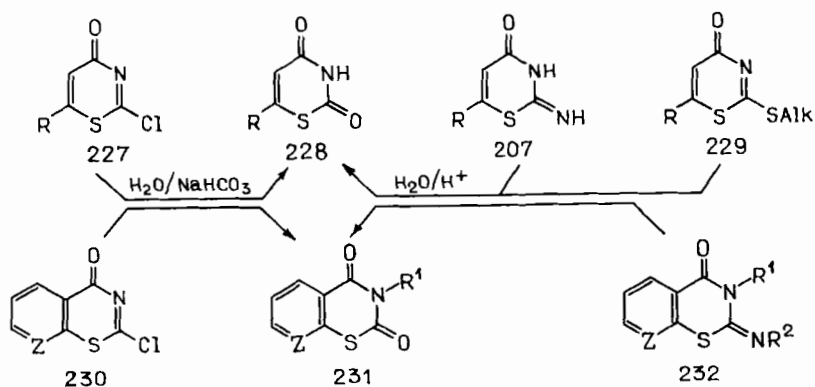
In comparison with monocyclic TAs, the benzo derivatives are more stable with respect to hydrolysis. However, ring opening and cleavage were observed in the reaction of 2-phenylbenzo-TA **76** with dilute sulfuric acid. The formation of dithio derivative **147** takes place due to the oxidation of intermediate 2-mercaptobenzamide by atmospheric oxygen (59BSF1791) (Scheme 85).

The basic hydrolysis of 2-chloro-TAs **227** (77LA1249) and **230** (70CB413) is a nucleophilic substitution that goes without ring opening to give diones **228** and **231**. The acid hydrolysis of 2-alkylthio-TAs **229** (66TL3225; 70AJC51) or 2-imino TAs **207** and their benzo (61GEP1096361, 61-USP2978448; 63ZOB213; 74GEP2218301) and pyrido derivatives **232** ( $\text{Z} = \text{CH, N}$ ) (73MI1) also gives dioxothiazines **228** and **231** ( $\text{Z} = \text{CH, N}$ ) and hence is widely used for their syntheses (Scheme 86).

Unlike the acid hydrolysis of iminobenzo-TAs, their basic hydrolysis (or methanolysis), as was shown for benzo-TA **233**, goes through an attack at



SCHEME 85



for 207, 227, 228, 229: R = H, Me, Ph, COOMe

for 230, 231: Z = CH; R<sup>1</sup> = H

for 231, 232: Z = CH; R<sup>1</sup> = H, Alk, CH<sub>2</sub>=CHCH<sub>2</sub>, CH<sub>2</sub>Ph, Ar, NH<sub>2</sub>;

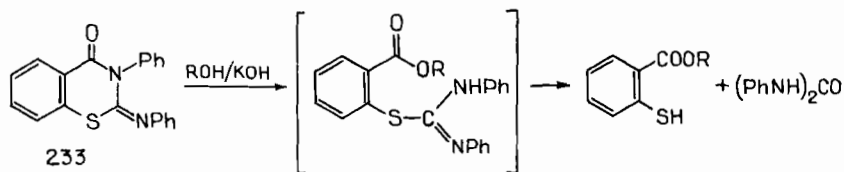
R<sup>2</sup> = H, Alk, Ar,  $\begin{array}{c} \text{NH} \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{NH}_2 \end{array}$ , CONH<sub>2</sub>, CONHAlk, CSNHAlk

for 231, 232: Z = N; R<sup>1</sup> = H, Alk; R<sup>2</sup> = H

SCHEME 86

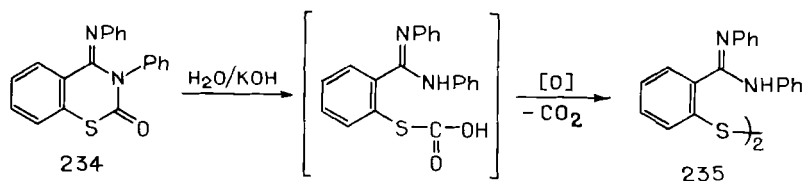
the 4 position of the heteroring to afford 2-mercaptobenzoic acid (or its ester) and diphenylurea (Scheme 87). By contrast, 4-iminobenzo-TA **234**, which is isomeric to benzo-TA **233**, reacts with hydroxide at the 2 position to afford amidine **235** (69PHA131) (Scheme 88).

2-Iminobenzo-TA **236** undergoes reversible ring opening with the formation of disodium salt **237** (64JOC761) (Scheme 89).

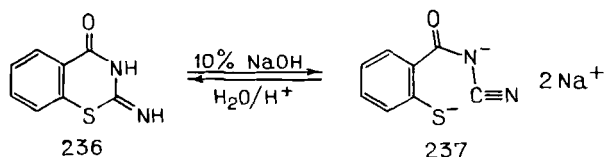


R = H, Me

SCHEME 87



SCHEME 88



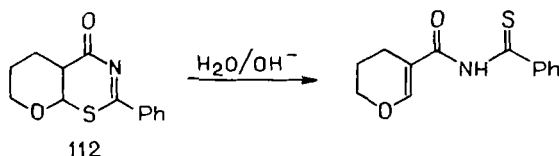
SCHEME 89

An unusual hydrolysis reaction was described for pyrano-TA **112**. In this case cleavage of the C—S bond common with the pyran ring took place (65CB3831) (Scheme 90).

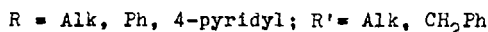
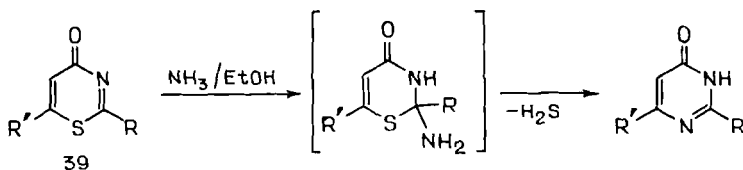
## 2. Reactions with Ammonia and Amines

One of the most important reactions of TAs is their transformation into pyrimidin-4-ones, which proceeds under the action of ammonia and amines according to the ANRORC mechanism. For thiazinones **39** it was suggested (81H851) that the first step is a nucleophilic addition of ammonia to the 2 position of the heterocyclic ring (Scheme 91).

However, 6-unsubstituted 2-alkylthio- or 2-imino-TAs undergo recyclizations via addition of amines or ammonia to the 6 position, as proved by the structure of the reaction products (64CIL1089; 70AJC51, 70CIL927) (Scheme 92).



SCHEME 90



SCHEME 91

In the case of TAs **39**, it is impossible to determine the position of the primary nucleophilic addition by the structure of reaction products; in order to define whether the 2 or 6 position is attacked, other evidence is necessary.

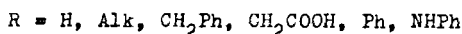
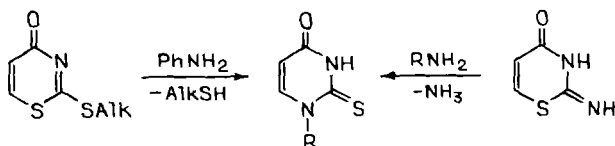
The reactions of 2-aryloxy- or 2-chloro-TAs **30** and **238** with amines do not give recyclization products. The interaction proceeds as a nucleophilic substitution to give 2-amino derivatives **237**. The action of the second mole of amines affords open-chain products **239** (85ZC430) and **240** (77LA1249), which are formed by nucleophilic attack at the 2 or 4 position of heterocycles **237** ( $R^2 = \text{H}$ ,  $R^3 = \text{CN}$ ,  $R^5 = \text{SMe}$ ) and **237** ( $R^3 = R^4 = \text{H}$ ), respectively (Scheme 93).

In comparison with monocyclic TA, their benzo derivatives are more stable with respect to ammonia and amines, but data on these reactions are sparse.

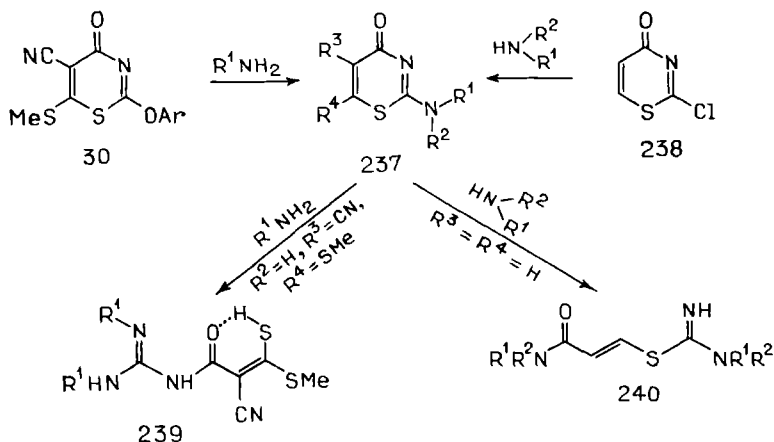
### 3. Reactions with Hydrazines and Hydroxylamine

The sole example of these reactions in the literature concerns the formation of 2,4-dinitrophenylhydrazones of benzo-TA **67** (63ZOB213).

In contrast to uncharged TAs, such protonated forms as perchlorates **206** easily react with hydrazines and hydroxylamine at the 2 position to give recyclization products—2-mercaptophenyl triazoles and oxadiazoles **241**—which show promise for use as ligands (91KGS1220) (Scheme 94).



SCHEME 92



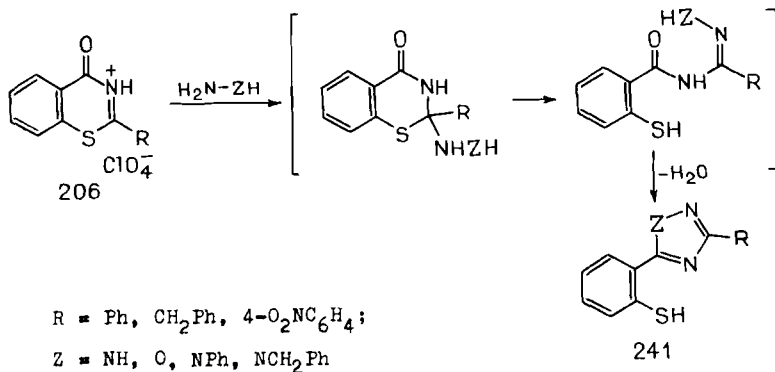
SCHEME 93

#### 4. Reactions with Alkylthioureas and Guanidines

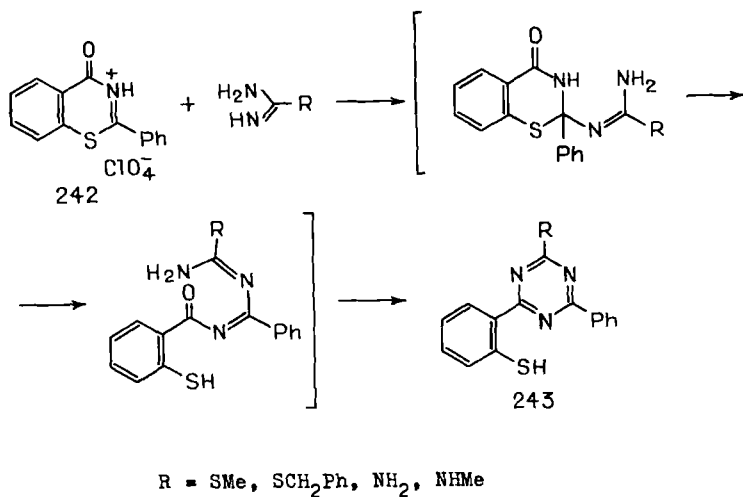
Thiazinonium perchlorate **242** also reacts at the 2 position of the heteroring with such 1,3-dinucleophiles as alkylisothioureas and guanidines. After recyclization, alkylmercapto- and aminotriazines **243** were obtained (87MI1) (Scheme 95).

#### 5. Reactions with Organomagnesium Compounds and Other C-Nucleophiles

2-Phenylbenzo-TAs **244** easily react with organomagnesium compounds to give products of nucleophilic attack at the 2 or 4 position. The direction



SCHEME 94



SCHEME 95

of addition depends on the structure of the *C*-anion. The most active alkylmagnesium halogenides give exclusively products of 2-addition **245**. Phenylmagnesium bromide reacts at the 4 position to give 4-phenyl-4-hydroxybenzothiazine **246**. Its structure was confirmed by the hydrolysis of its hydrochloride **248** into the well known 2-mercaptobenzophenone **250**. The Ritter reaction of the latter with benzonitrile gives an initial hydrochloride **248**. Benzylmagnesium chloride reacts at the 4 position to afford hydroxybenzothiazine **247** and 4-benzylidenebenzothiazine **249** (75CB2523; 76ACH61) (Scheme 96).

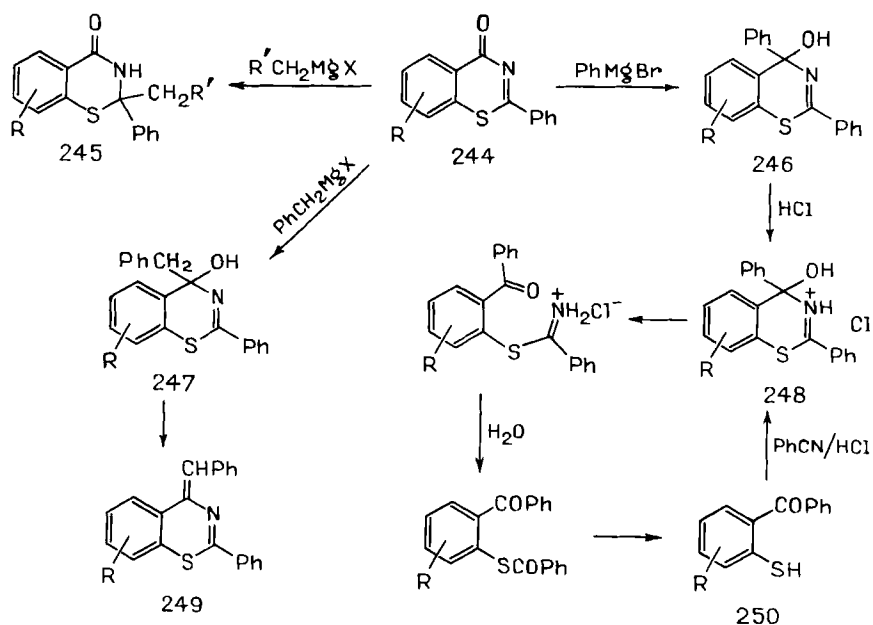
The reaction of 2-chlorobenzo-TA **230** with methylene-active compounds in the presence of bases leads to olefins **251** and **252** (70CB413) (Scheme 97).

## 6. Reduction

The reduction of TAs **39** with  $\text{NaBH}_4$  or  $\text{LiAlH}_4$  affords the products of hydrogen addition to the  $\text{C}=\text{N}$ -bond, **253** (73MI1; 81H851) (Scheme 98). The reduction of benzo-TA **254** by aluminum amalgam also gives 2,3-dihydro derivatives **255** (53AP437).

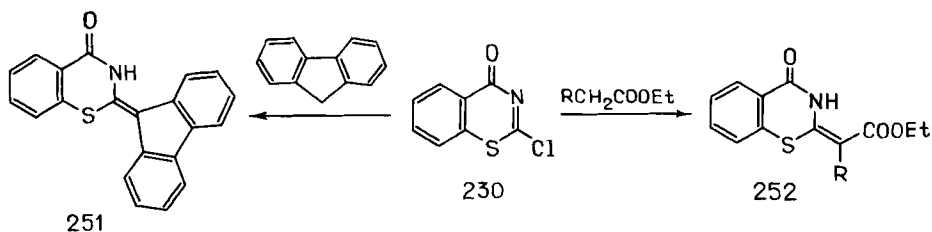
Hydrogenation of benzo-TA **254** by hydrogen *in situ* in  $\text{Sn}/\text{HCl}$  leads to the ring cleavage and the formation of 2-mercaptobenzoic acid and arylamides (60MI1) (Scheme 99).

The carbonyl group of 2,2-disubstituted 2,3-dihydrobenzo-TAs **256** may be reduced into a  $\text{CH}_2$  group by the action of  $\text{LiAlH}_4$  (66CR77;



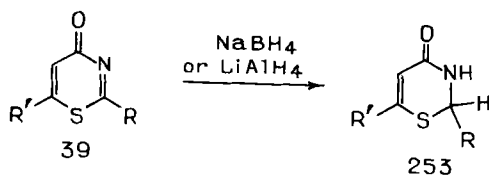
$R = H; 6,7-(OMe)_2$ ;  $R' = Me, n-C_3H_7$ ;  $X = Cl, Br$

SCHEME 96



$R = CN, COOEt$

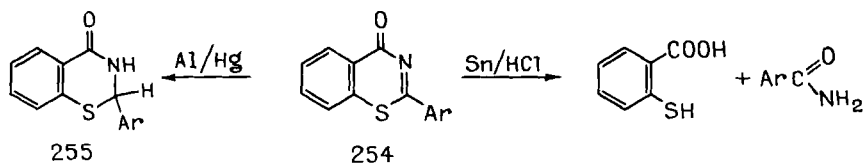
SCHEME 97



$R = Alk, Ph, 4\text{-pyridyl}$ ;  $R' = Alk, CH_2Ph$

SCHEME 98

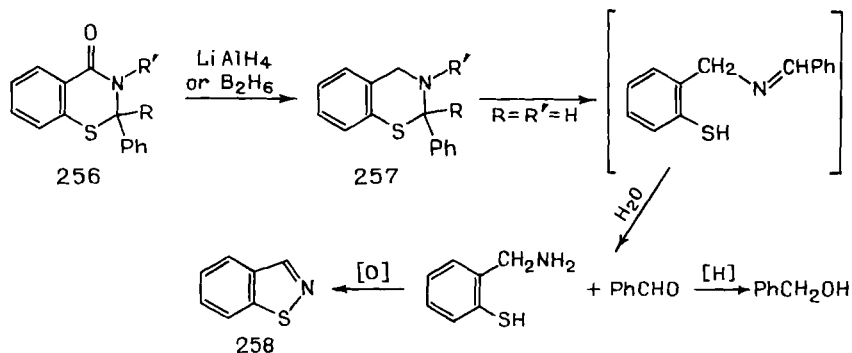




SCHEME 99

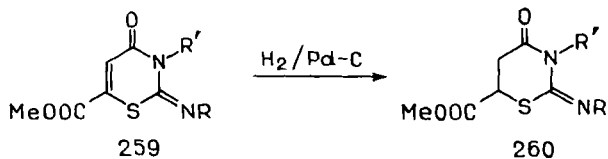
69USP3455915; 71CR372; 72BRP1275593) or diborane (69USP3455915). The same reaction of 2-phenyl-2,3-dihydrobenzo-TA **256** ( $R = R' = H$ ), in contrast to the 2,2-disubstituted derivatives, gives a mixture 2,3-dihydrobenzothiazine **257** and products of its further degradation—2-mercaptobenzylamine, benzothiazole **258**, and benzyl alcohol (67CR1304) (Scheme 100).

Catalytic hydrogenation of imino-TAs **259** leads to the reduction of the  $C=C$ -bond to give 5,6-dihydro-TAs **260** (67CJC939) (Scheme 101).



$R = H, \text{Alk}; R' = H, N\text{-subst. aminoalk.}$

SCHEME 100



$R, R' = H, \text{Alk}, \text{PhCH}_2, \text{Ar}$

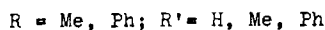
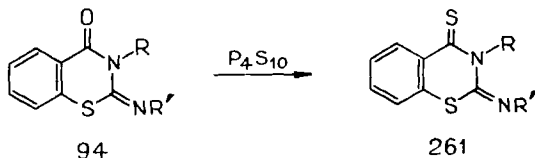
SCHEME 101

### 7. Reactions with Phosphorus Pentasulfide

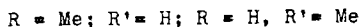
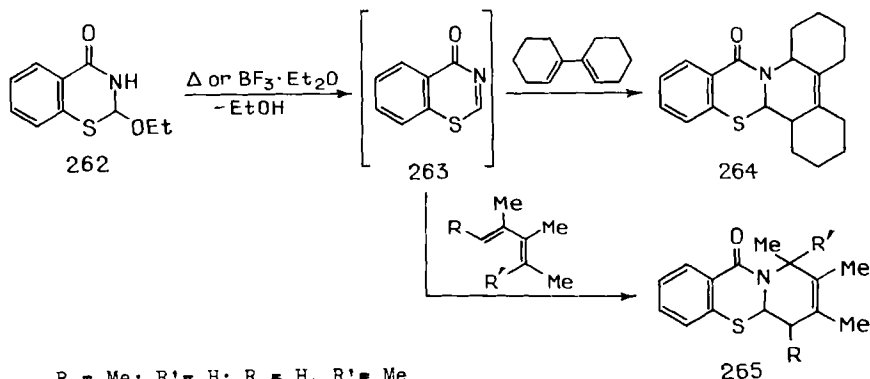
The carbonyl portion of 2-iminobenzo-TA **94** can be converted into the thioxo group with the formation of derivatives **261** (67PHA611) (Scheme 102). The analogous reactions are also known for monocyclic 1,3-thiazin-4-ones (67CJC939) and for 2,3-dihydro-1,3-benzothiazin-4-ones (55BSF-1518).

### D. REACTIONS WITH CYCLIC TRANSITION STATES

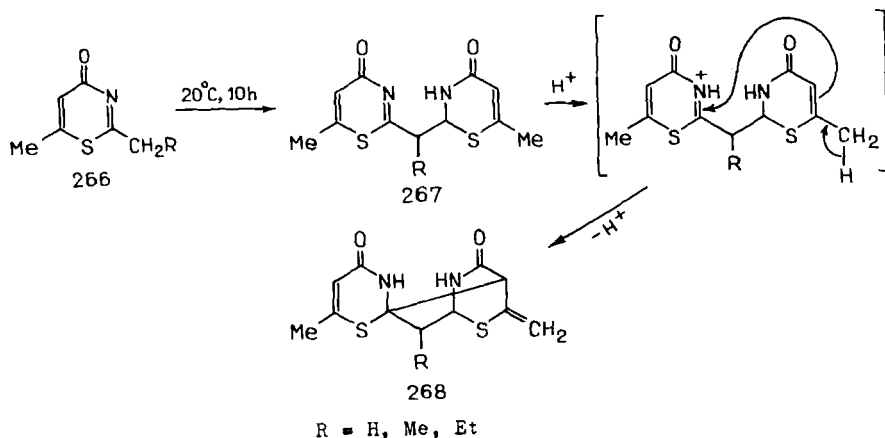
The unsubstituted benzo-TA **263** that was generated *in situ* from 2-ethoxy-2,3-dihydrobenzo-TA **262** reacts with 1,3-dienes to give the Diels-Alder adducts **264** and **265** (73JHC149) possessing a *cis*-configuration according to the Woodward-Hoffmann rules for [2 + 4]-cycloaddition (Scheme 103).



SCHEME 102



SCHEME 103

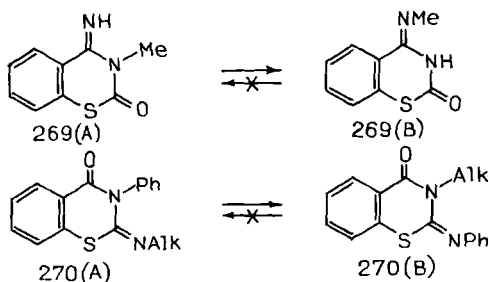


SCHEME 104

## E. REACTIVITY OF SUBSTITUENTS

The electron-acceptor influence of S and N atoms increases the C—H acidity of 2-alkyl groups. Thus, 2-alkyl-TAs **266** undergo a spontaneous dimerization both in solution and during storage to give **267**. Under acid-catalytic conditions, dimerization gives spirocyclic compounds **268** in quantitative yield [83CPB1936, 83JCS(CC)56] (Scheme 104).

On melting or heating in the presence of ammonia or primary amines, 4- and 2-imino-TAs **269** and **270** undergo Dimroth rearrangement with the formation of a thermodynamically more stable isomer. For TAs **270** possessing substituents on two N atoms, the energetically favorable isomers are those having electron-donor substituents on the endocyclic N atom (67ZC231; 69PHA100) (Scheme 105).



SCHEME 105

## IV. Applications

Progress in the chemistry of 1,3-thiazin-4-ones is mainly attributable to their applications in the pharmaceutical area. In the search for new drugs, the most intensive investigation has focused on the modification of substituents in the thiazinone ring and in the syntheses of thiazinones fused with heterocycles.

A large number of papers and patents deal with the biochemical properties of these compounds. In addition to the applications described in the previous sections of this review, TAs are known as analgesics (69USP3470168; 74JAP73/31114; 79JAP79/20504), tranquilizers (69USP-3459748; 84POP122833; 91MI1), and antidepressants (71GEP1926071; 72BRP1275593). They are also depressants (69USP3455915; 81MI1) of the central nervous system, psychostimulants (72FRP2047871), anticonvulsants (85FES58), antimicrobial agents (89USP4839356), and fungicides (62GEP1079050; 74GEP2218301, 74GEP2218362, 74JAP73/02771; 76AP161; 79JAP79/20504). Some thiazinone derivatives are used as anti-irradiation agents (64JOC224; 66JIC37), while others serve as components of cosmetics (81GEP2938418). 5-Aryl-TAs may be used as pesticides and herbicides (94GEP4243818), and 2,3-dihydro-TAs are considered to be potential antipsychotic agents (93JMC3417). Recently, *N*-(nitrooxyalkyl)-benzothiazinediones have become the subject of great interest as cardiovascular agents (92EUP490183; 94EUP566018, 94WOP25542).

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# Synthesis, Chemistry, and Biological Properties of Thienopyrimidines

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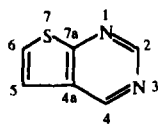
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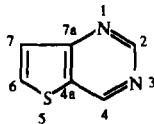
## I. Introduction

### A. NOMENCLATURE

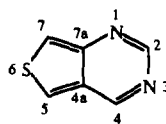
For the nomenclature of thienopyrimidines the system in *Chemical Abstracts* has been universally adopted. There are three isomeric thienopyrimidine systems **I–III**.



(I) [2,3-d]



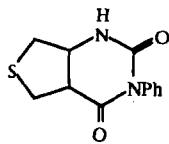
(II) [3,2-d]



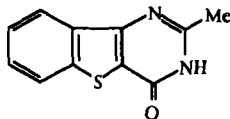
(III) [3,4-d]

### B. BACKGROUND

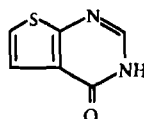
The first derivative of any of these ring systems was the thieno[3,4-*d*]pyrimidine **IV** reported by Baker *et al.* in 1947 (47JOC174). A year later McClelland and Stammers (48JCS78) published the synthesis of the first thieno[3,2-*d*]pyrimidine (**V**). Then in 1953, Baker *et al.* (53JOC138) described the preparation of the first thieno[2,3-*d*]pyrimidine **VI**.



(IV)



(V)



(VI)

Very little interest in the subject was shown until the late 1960s when Roth (69JMC227) undertook studies in chemotherapy based on inhibition of folate biosynthesis and function by certain 2,4-diaminothieno[2,3-*d*]pyrimidines. Since then, a continuous effort directed toward the preparation

of biologically active compounds has led to a remarkable development of thienopyrimidine chemistry.

The intention of this review is to update the literature since the publication of the chapter on thienopyrimidines in the major work of Katritzky and Rees (84MI1). Various aspects of the chemistry and biology of thienopyrimidines are covered in the book of Gronowitz (85MI2) and in the reviews by Melik-Ogandzhanyan (85UK450) and Unverferth (90PHA545). In the present review, an effort is being made to group the ring syntheses according to the type of starting material used and thienopyrimidine produced. The primary chemical literature up to April 1995 has been searched.

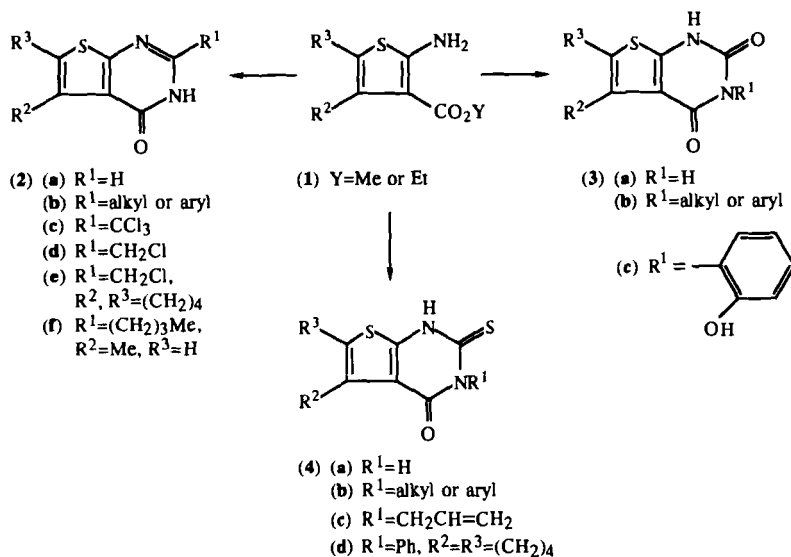
## II. Thieno[2,3-*d*]pyrimidines

### A. SYNTHESIS

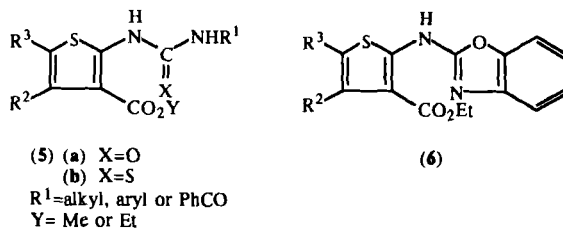
#### 1. From Thiophenes

a. *From Alkyl 2-Aminothiophene-3-carboxylates.* By far the most widely used method for the synthesis of thieno[2,3-*d*]pyrimidines is condensation of 2-aminothiophene-3-carboxylates **1** with reagents that provide the remaining C—N fragment required for pyrimidine fusion. Thus, heating thiophenes **1** in formamide at 200°C (81JHC1277; 83MI1; 84MI2; 86KFZ39; 93PHA192) provided directly 2-unsubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **2a**; with urea (90EUP404356; 94JHC305), thieno[2,3-*d*]pyrimidine-2(1*H*),4(3*H*)-diones **3a**; and with alkyl aryl isocyanates [80JCS(P1)1853; [94MI1], 3-alkyl- or 3-arylthieno[2,3-*d*]pyrimidine-2,4-diones **3b**. When potassium thiocyanate in the presence of gaseous hydrochloric acid or formamide and sulfur [90EUP404356, 90IJC(B)1070, 90MI22] was reacted with thiophenes **1**, thieno[2,3-*d*]pyrimidin-4-one-2-thiones **4a** resulted. Ram and Pandey (81JHC1277) and Fedorova *et al.* (86KFZ39) obtained 3-phenyl- or benzylthieno[2,3-*d*]pyrimidin-4(3*H*)-one-2(1*H*)-thiones **4b** by heating ethyl 2-aminothiophene-3-carboxylates **1** with phenyl or benzyl isothiocyanates at 160–180°C, respectively. Sukumaran and Rajasekharan [89IJC(B)642] used milder conditions to synthesize twenty 3-alkyl or 3-aryl derivatives of **4b** from *o*-aminocarboxylates **1**. The latter required stirring with alkyl or aryl isothiocyanates in DMF and base at room temperature. Benzoylthiourea **5b**, derived from *o*-aminocarboxylates **1** and benzoyl isothiocyanate, were cyclized with dilute solution hydroxide and treated with various alkyl halides to give directly 2-alkylthio compounds **2c** (89AP322). 3-Allylthieno[2,3-*d*]pyrimidin-4-one-

2(1*H*)-thiones **4c** were obtained by heating *o*-aminocarboxylates **1** with allyl isothiocyanate followed by treatment with sodium hydroxide (89CPB2122).

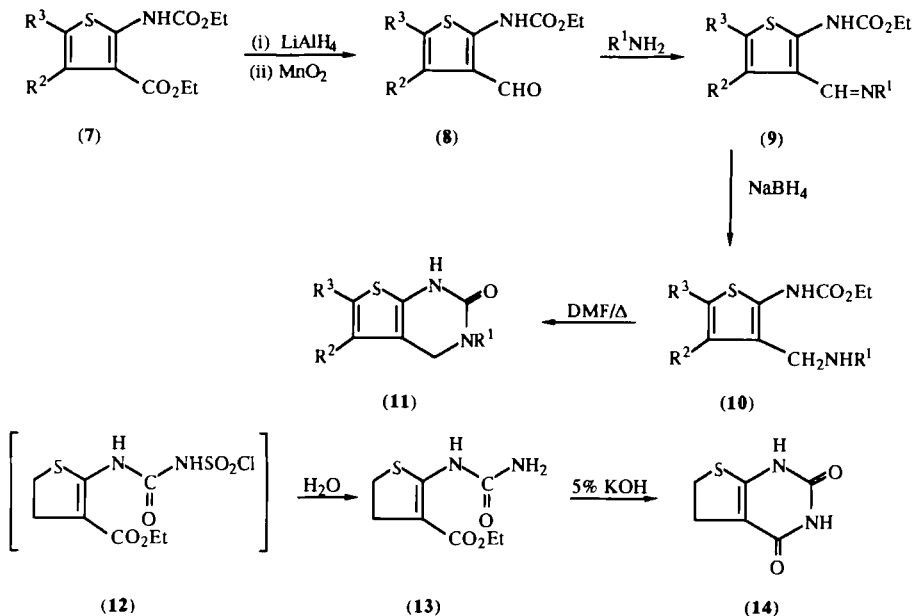


Several syntheses of thieno[2,3-*d*]pyrimidine-2,4-diones **3** -pyrimidin-4-one-2-thiones **4** from thiophenes **1** proceed via isolable intermediates. Thus alkyl and aryl isocyanates (88JMC1786; 89USP835157; 90PHA493; 91MI1; 94MI1) reacted with **1** to give ureas **5a**, which were then cyclized in base into thieno[2,3-*d*]pyrimidine-2,4-diones **3b**. Ethyl 2-[(2-benzoxazolyl)amino]thiophene-3-carboxylates **6** obtained from thiophenes **1** and 2-chlorobenzoxazole was simultaneously hydrolyzed and cyclized to 3-(2-hydroxyphenyl)thienopyrimidine-2(1*H*),4-diones **3c** by heating in ethanolic potassium hydroxide (94MI1). Another synthetic approach to the 3-substituted thieno[2,3-*d*]pyrimidine-2,4-dione ring system **3b** has been reported. *o*-Aminoesters **1** reacted with phosgene to give intermediate alkyl



2-isocyanothiophene-3-carboxylates, which were converted into ureas **5a** by reaction with amines and then cyclized in DMF containing base to the products **3b** [89EUP311321, 89MIP1; 90JAP(K)225485].

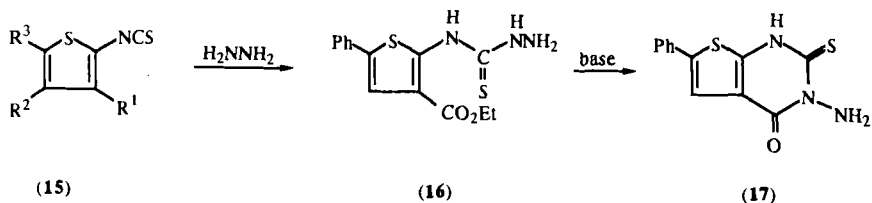
Carbamate intermediate **7** derived from aminothiophenes **1** and ethyl chloroformate were converted into 3-substituted thieno[2,3-*d*]pyrimidine-2,4-diones **3b** by cyclocondensation with amines [89CPB2091, 89JAP(K)213284, 89MIP1; 93MI1]. In a variation of this reaction, the 3-ethoxycarbonyl group of carbamates **7** was reduced to hydroxymethyl with lithium aluminum hydride and then oxidized with manganese(IV) oxide to give aldehydes **8**. Reaction of these aldehydes with amines afforded Schiff's bases **9**. The latter were reduced by sodium borohydride to amino-methylthiophenes **10**, which cyclized into 4*H*-thieno[2,3-*d*]pyrimidin-2(1*H*)-ones **11** [89CPB2717, 89JAP(K)242587] by heating in DMF. Ethyl 2-amino-4,5-dihydrothiophene-3-carboxylate, upon reaction with chlorosulfonyl isocyanate in absolute dichloromethane followed by hydrolysis of the intermediate chlorosulfonyl urea **12**, gave ethyl 2-aminocarbonylamino-4,5-dihydrothiophene-3-carboxylate **13**. The latter was cyclized in base into 5,6-dihydrothienopyrimidine-2(1*H*),4(3*H*)-dione **14** (85S190).



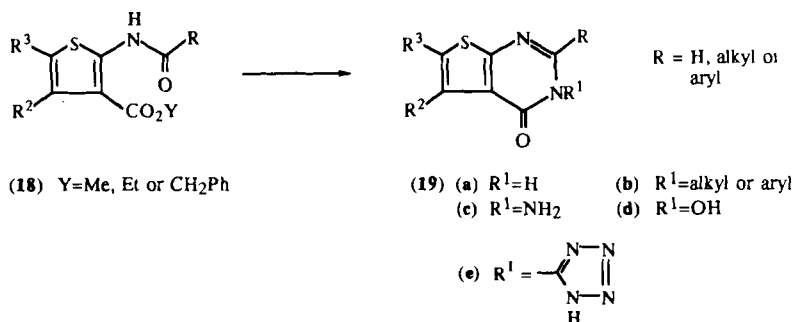
Reaction of thiophenes **1** with alkyl or aryl isothiocyanates gave the corresponding thiourea derivatives **5b**, which were cyclized in base and



then acidified to afford thieno[2,3-*d*]pyrimidin-4-one-2(1*H*)-thiones **4b** [81JIC(B)538; 85EUP144101; 86GEP240892; 87PHA160; 89AP322; 90MI3, 90PHA827]. In a slight modification of this route, isothiocyanates **15**, prepared from aminothiophenes **1** and thiophosgene, were treated with amines to give thiourea derivatives **5b**, which were cyclized into thieno[2,3-*d*]pyrimidin-4-one-2(1*H*)-thiones **4b** (83HCA148; 89CPB2122; 90PHA827). 3-Amino-6-phenylthieno[2,3-*d*]pyrimidin-4-one-2(1*H*)-thione (**17**) was obtained similarly from isothiocyanate **15** ( $R^1 = \text{CO}_2\text{Et}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{Ph}$ ) via the thiosemicarbazide **16** (94PHA64). Isothiocyanate **15** [ $R^1 = \text{COPh}$ ,  $R^2, R^3 = (\text{CH}_2)_4$ ] was reacted with hydrazine hydrate and various primary amines to give directly the 3-substituted 4-phenyl-2-thioxothieno[2,3-*d*]pyrimidines **82b** (90JHC269).



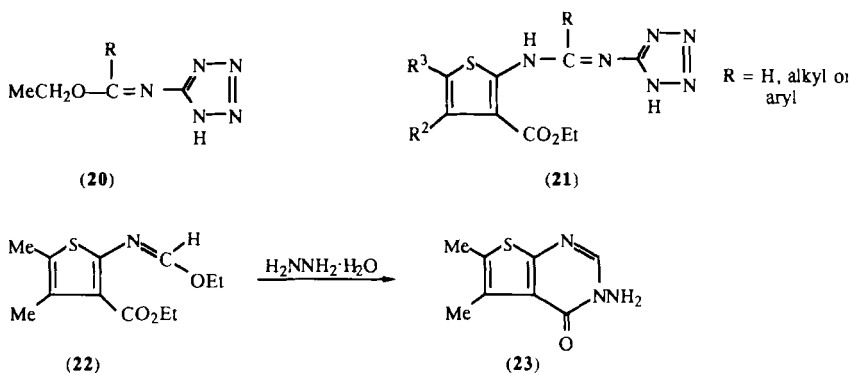
Intermediate alkyl 2-acylaminothiophene-3-carboxylates **18**, derived from reacting 2-aminothiophenes **1** with acids, acid chlorides, or acid anhydrides, are cyclocondensed with acetic acid and formamide (83ZC179), ammonium formate and formamide (86MI1), ammonia (89PHA860; 92PHA577), amines [81CS135; 86GEP240891; 87JAP(K)132884; 88JAP(K)126884], hydrazine hydrate (81CS135, 81KFZ40; 88MI1; 92MI2), or hydroxylamine hydrochloride [81JAP(K)8389, 81JAP(K)53681, 81JAP(K)56389, 81JAP(K)59778, 81JAP(K)81010] to the corresponding thieno[2,3-*d*]pyrimidin-4-ones **19a-d**.



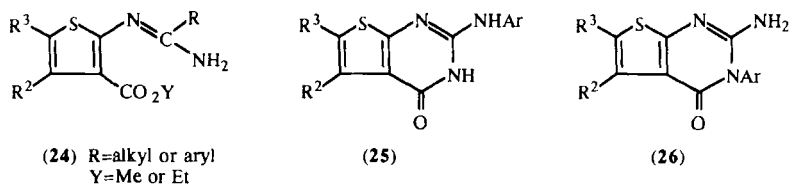
Hanbold *et al.* (83PHA269) prepared 2-arylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **19a** by treating *o*-aminocarboxylates **1** with imidates in a mixture of chlorobenzene and PPA.

Amidines **21** derived from imidates **20** and thiophenes **1** were cyclized into 3-(1*H*-tetrazol-5-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **19e** by refluxing in an aqueous mixture of sodium hydroxide and propan-2-ol (87EUP234557).

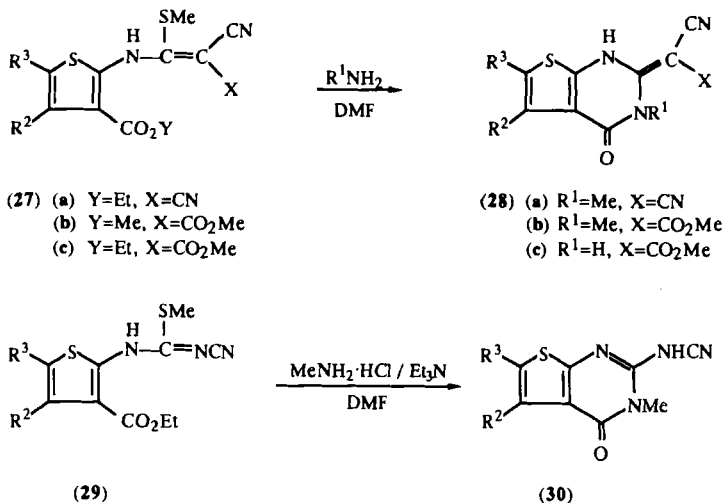
Ethyl 2-amino-4,5-dimethylthiophen-6-carboxylate heated under reflux with triethyl orthoformate gave ethyl 2-ethoxymethyleneimino-4,5-dimethylthiophene-3-carboxylate **22** resulted. Reaction of the latter with hydrazine hydrate gave 3-amino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-one **23** [85IJC(B)432].



Amidines **24** are considered as possible intermediates in the condensation of *o*-aminoesters **1** with aliphatic or aromatic nitriles in the presence of dry hydrogen chloride en route to thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **2b** [82IJC(B)666; 88MI1; 89IJC(B)1039; 92EUP502725; 93PHA192]. The same reaction has been successful with various nitrile derivatives such as  $\alpha$ -functionalized acetonitrile compounds [83INP151496; 85JHC825; 86GEP234268, 86GEP234269, 86GEP234270; 87JHC581; 87USP4701528; 89PHA790; 90AF567, 90IJC(B)1070], phenyl cyanate, alkyl and aryl thiocyanates, cyanamide, aryl, cyanamides, *N*-cyanomorpholine, and acyl cyanides [83IJC(B)76; 84JHC375; 87JHC581; 90AF567]. *N*-Arylcyanamides with *o*-aminoesters **1** afforded a mixture of isomeric 2-aminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **25** and **26**.



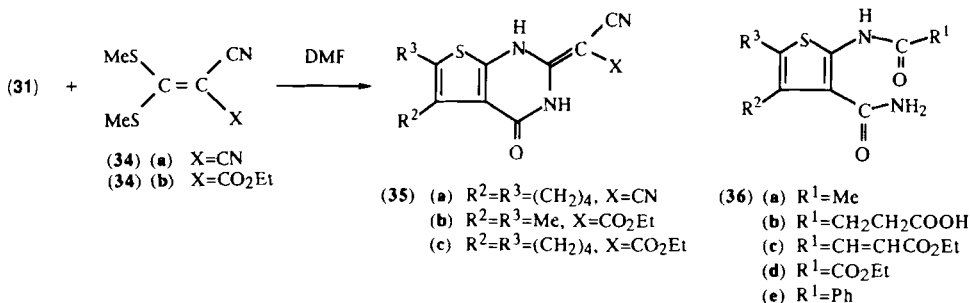
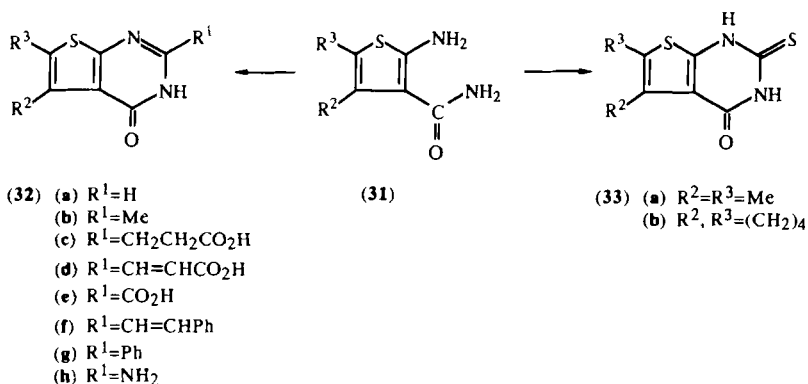
By treating aminothiophenes **1** with 3,3-bismethylthio-2-(cyano)acrylonitrile or methyl 3,3-bismethylthio-2-(cyano)acrylate in dimethylformamide (DMF) containing sodium carbonate, the corresponding 3-(thien-2-yl)-amino-2-cyano-3-methylthioacrylonitriles **27a** and methyl 3-(thien-2-yl)-amino-2-cyano-3-methylthioacrylates **27b** were obtained (87GEP249020, 87GEP249022; 89PHA348). The cyclization of acrylonitriles **27a** to 2-cyano-2(3-methylthieno[2,3-*d*]pyrimidin-2-ylidene)acetonitriles **28a** was conducted by refluxing the former with methylamine hydrochloride in a mixture of DMF and ethanol containing triethylamine. On the other hand, the acrylates **27b**, when treated at ambient temperature with methylamine hydrochloride in this solvent mixture, gave better yields of methyl 2-cyano-(3-methylthienopyrimidin-2-ylidene)acetates **28b**. Several derivatives of acrylates **27c** were converted into 2-cyano(thienopyrimidin-2-ylidene)acetates **28c** by reaction with ammonia solution (89PHA348). The latter solvent mixture and temperature conditions were also used to prepare imines **29** from a mixture of **1** and dimethyl cyanodithioiminocarbonate. Imines **29** and methylamine hydrochloride were refluxed in the same solvent mixture to give *N*-(thieno[2,3-*d*]pyrimidin-2-yl)cyanamides **30** (87GEP249023).



b. *From 2-Aminothiophene-3-carboxamides and Thiocarboxamides.* 2-Aminothiophene-3-carboxamides and thiocarboxamides require a one-carbon unit from a double electrophilic reagent for ring closure to thieno[2,3-*d*]pyrimidines.

2-Unsubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **32a** were directly formed by heating carboxamides **31** in formic acid (86M14; 91EUP447891)

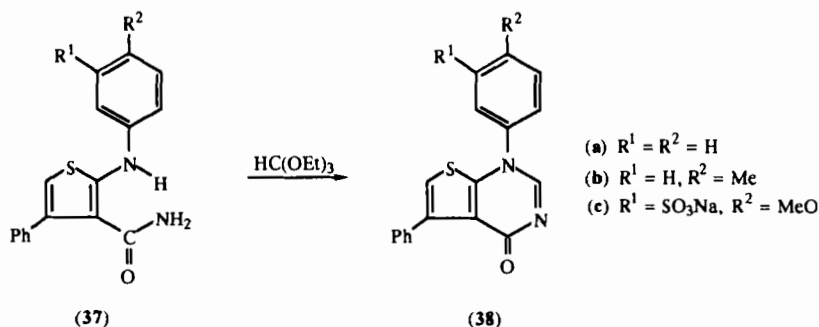
or triethyl orthoformate (89EUP329168). When carboxamides **31** were reacted with acetylacetone (84MI2), cinnamaldehyde (85JHC825), benzoin (90MI1), or trichloroacetonitrile (89ZN488), the 2-substituted derivatives **32b, f-h** were isolated. Melting each carboxamide **31** [ $R^2 = R^3 = \text{Me}$  or  $(\text{CH}_2)_4$ ] with thiourea produced the corresponding thieno[2,3-*d*]pyrimidin-4(3*H*)-one-2(1*H*)-thiones **33a** and **33b**.



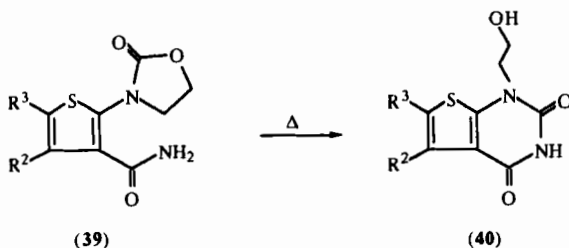
The reaction between carboxamide **31** [ $R^2 = R^3 = (\text{CH}_2)_4$ ] and 3,3-bismethylthio-2-cyanoacrylonitrile **34a** in refluxing DMF containing sodium carbonate, gave 2-cyano-2-(thieno[2,3-*d*]pyrimidin-2-ylidene)acetonitrile **35** in 69% yield. Under the same reaction conditions, each carboxamide **31** [ $R^2 = R^3 = \text{Me}$  or  $(\text{CH}_2)_4$ ] reacted with methyl 3,3-bismethylthio-2-cyanoacrylate **34b** and gave good yields of 2-cyano-2-(thieno[2,3-*d*]pyrimidin-2-ylidene)acetates **35b** and **35c**, respectively (87GEP249020).

The isolation of diamides **36a-c** occurred when carboxamides **31** were reacted with acetic anhydride (89YZ464; 93PHA342), succinic anhydride (86GEP240891; 89PHA860; 90EUP349239), diethyl fumarate, diethyl oxalate (81GEP152129), or benzoyl chloride (89YZ464). Cyclization of each diamide in base gave the corresponding 2-substituted thieno[2,3-*d*]-pyrimidin-4(3*H*)-ones **32b-e, g**.

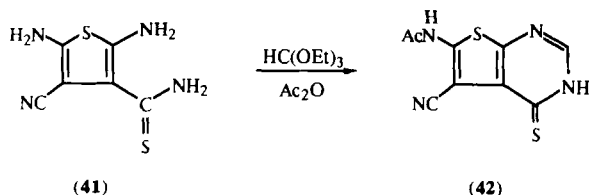
1-Arylthieno[2,3-*d*]pyrimidin-4-ones **38a-c** were obtained by heating the 2-arylaminothiophene-3-carboxamides **37a-c** with triethyl orthoformate (84JPR917).



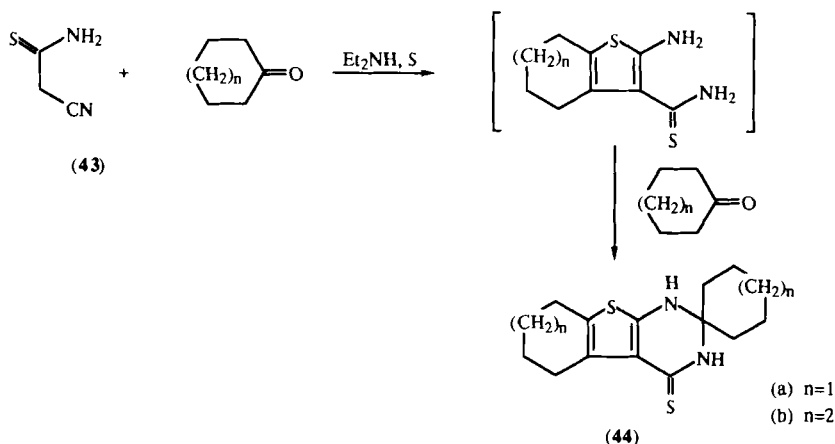
Intramolecular cyclization of 4,5-dihydro-3-(2-thienyl)-oxazol-2-ones **39** gave 1-hydroxyethylthieno[2,3-*d*]pyrimidine-2,4(3*H*)-diones **40** [89JAP(K)242587]. The latter compounds were also obtained directly from carboxamides **31** by reaction with 2-chloroethyl chloroformate followed by treatment with ethanolic potassium hydroxide (89H985).



2-Aminothiophene-3-thiocarboxamide **41** was converted into the thieno[2,3-*d*]pyrimidine-4(3*H*)-thione **42** by heating in a mixture of acetic anhydride and triethyl orthoformate.

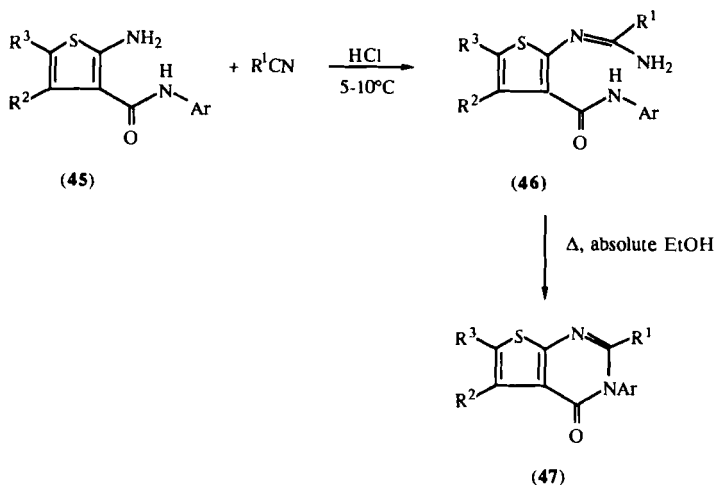


In a one-pot reaction, cyanothioacetamide **43** reacted with cyclic ketones and sulfur in the presence of a diethylamine catalyst to give the 2-spirothieno[2,3-*d*]pyrimidine-4(3*H*)-thiones **44** in moderate yields (90JPR223).



c. *From 2-Aminothiophene-3-carboxanilides.* In reactions involving *o*-aminoanilides **45**, the remaining one-carbon unit for ring closure to 2-substituted 3-*N*-arylthieno[2,3-*d*]pyrimidin-4-ones **47** is provided by nitrile derivatives. Although the synthesis of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **2b** was postulated to occur via amidine intermediates **24** (see Section II.A.1.a), these amidines have not been isolated. Shishoo *et al.* [89IJC(B)1039] managed, however, to isolate the first amidines **46** by reacting *o*-aminoanilides **45** with acetonitrile or *p*-chlorophenylacetonitrile at 5–10°C under acidic conditions. The amidines **46** were found to cyclize in refluxing ethanol without acid to give 3-*N*-arylthienopyrimidin-4-ones **47**, and with acid as a catalyst to give thienopyrimidin-4(3*H*)-ones **2b**.

Further examples of 2-cyano-2-(thieno[2,3-*d*]pyrimidin-2-ylidene) acetates **28a** ( $R^1 = \text{Ph or Ar}$ ) and -acetonitriles **28b** ( $R^1 = \text{Ph or Ar}$ ) (see

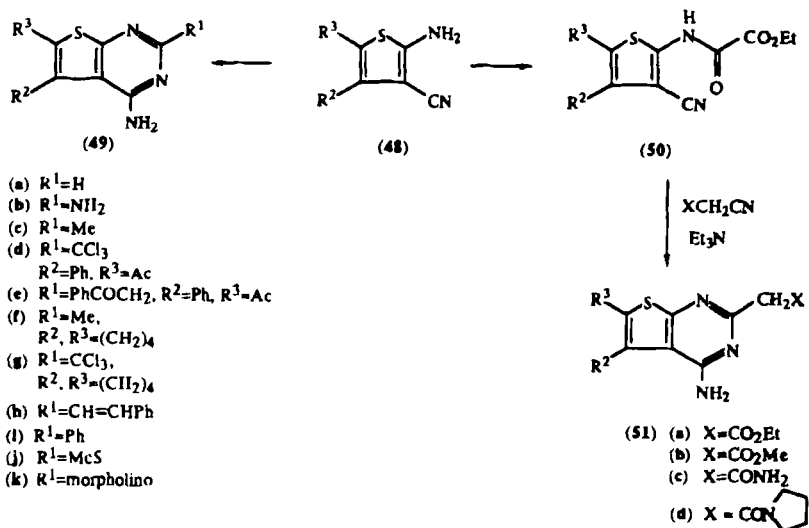


Section II.A.1.a) were obtained (87GEP249021; 89PHA348) by direct reaction of anilides **45** with methyl 3,3-bismethylthio-2-cyanoacrylate or 3,3-bismethylthio-2-cyanoacrylonitrile, respectively.

d. *From 2-Aminothiophene-3-carbonitriles.* Like alkyl 2-aminothiophene-3-carboxylates, 2-aminothiophene-3-carbonitriles also require a C—N fragment to form the pyrimidine ring. The main difference is that the nitrile group is transformed into an amino or imino group at position 4 of the formed thieno[2,3-*d*]pyrimidine.

A widely used method of preparing 3-amino-2-unsubstituted thieno[2,3-*d*]pyrimidines **49a** is by condensing *o*-aminocarbonitriles **48** with formamide (83MI1; 86KFZ39; 88JPR585; 89MI2; 90MI5). On the other hand, 2,4-diaminothieno[2,3-*d*]pyrimidines **49b** were formed by condensing *o*-aminocarbonitriles **48** with various reagents such as urea or thiourea (88JPR585; 92PS93), guanidine (90HCA797; 92PS93), and chloroformamide hydrochloride (93JMC3103). In the latter reaction, aminocarbonitriles **48** and chloroformamide hydrochloride had to be copulverized and mixed thoroughly at  $120^\circ C$  for best results. Diamines **49b** were also synthesized by heating *o*-aminocarbonitriles **48** with carbon disulfide to give thieno[2,3-*d*]pyrimidine-2(1*H*),4(3*H*)-dithiones **71** followed by treatment of the dithiones with ammonia solution (90HCA797).

Several 4-amino-2-methylthieno[2,3-*d*]pyrimidines **49c** were synthesized directly by heating *o*-aminocarbonitriles **48** in a methanolic solution of acetamide hydrochloride containing sodium ethoxide (83CPB1177). By an indirect route, 4-amino-2-substituted methyl-5,6-dihydrothieno[2,3-*d*]-



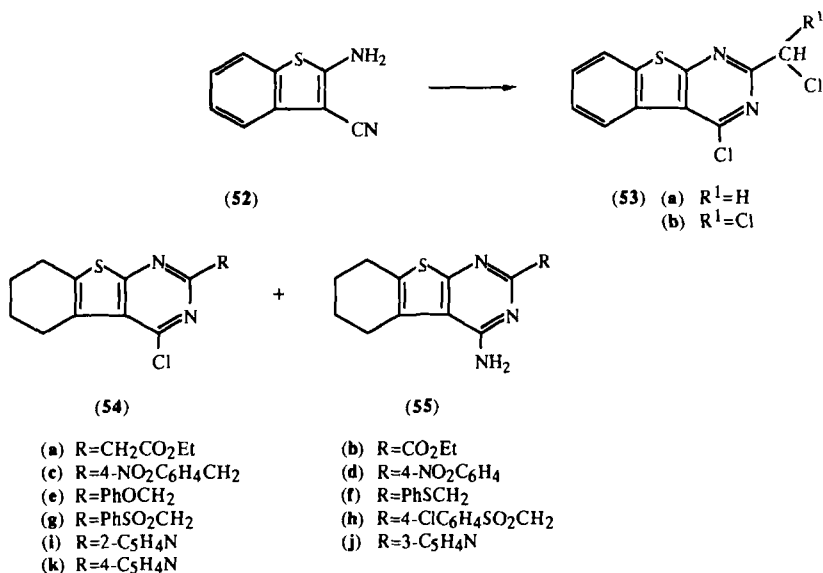
pyrimidines **51a–d** were obtained by heating ethyl *N*-(3-cyano-4,5-dihydro-2-thienyl)oxamates **50** with ethyl or methyl cyanoacetate,  $\alpha$ -cyanoacetamide, or 1-cyanoacetylpyrrolidine in the presence of triethylamine (83CPB1177). 6-Acetyl-4-amino-5-phenyl-2-trichloromethylthieno[2,3-*d*]-pyrimidine **49d** was obtained quantitatively by heating *o*-aminocarbonitrile **48** ( $R^2 = \text{Ph}, R^3 = \text{Ac}$ ) with trichloroacetonitrile in dry benzene containing a catalytic amount of piperidine (89ZN488). Similarly *o*-aminonitrile **48** ( $R^2 = \text{Ph}, R^3 = \text{Ac}$ ) and benzoylacetonitrile in DMF gave the 2-benzoylmethyl derivative **49e** (92AP301).

Under different reaction conditions, i.e., bubbling hydrogen chloride gas into a dioxane solution of *o*-aminocarbonitrile **52**, the reaction with acetonitrile gave 4-amino-2-methylthieno[2,3-*d*]pyrimidine **49f** (90JHC119), and with trichloroacetonitrile, the 4-amino-2-trichloromethylthieno[2,3-*d*]pyrimidine **49g** (89ZN488). Similarly, when nitriles such as cinnamonnitrile (85JHC825), phenylacetonitrile, benzonitrile, methyl thiocyanate, and cyanomorpholine (89ZN488; 90JHC119; 92AP301) are reacted with *o*-aminocarbonitriles **48**, the corresponding 4-amino-2-substituted thieno[2,3-*d*]pyrimidines **49h–k** are formed.

When chloro- and dichloroacetonitriles were reacted with *o*-aminocarbonitrile **52**, 4-chloro-2-chloromethyl- and 4-chloro-2-dichloromethylthieno[2,3-*d*]pyrimidines **53a** and **53b** were obtained, respectively. For compounds with stronger electron-withdrawing substituents on the  $\text{C}\equiv\text{N}$  group, such as ethyl cyanoacetate, ethyl cyanoformate, 4-nitrobenzylcyanide, 4-nitrobenzonitrile, phenoxyacetonitrile, phenylthioacetonitrile, phenylsul-

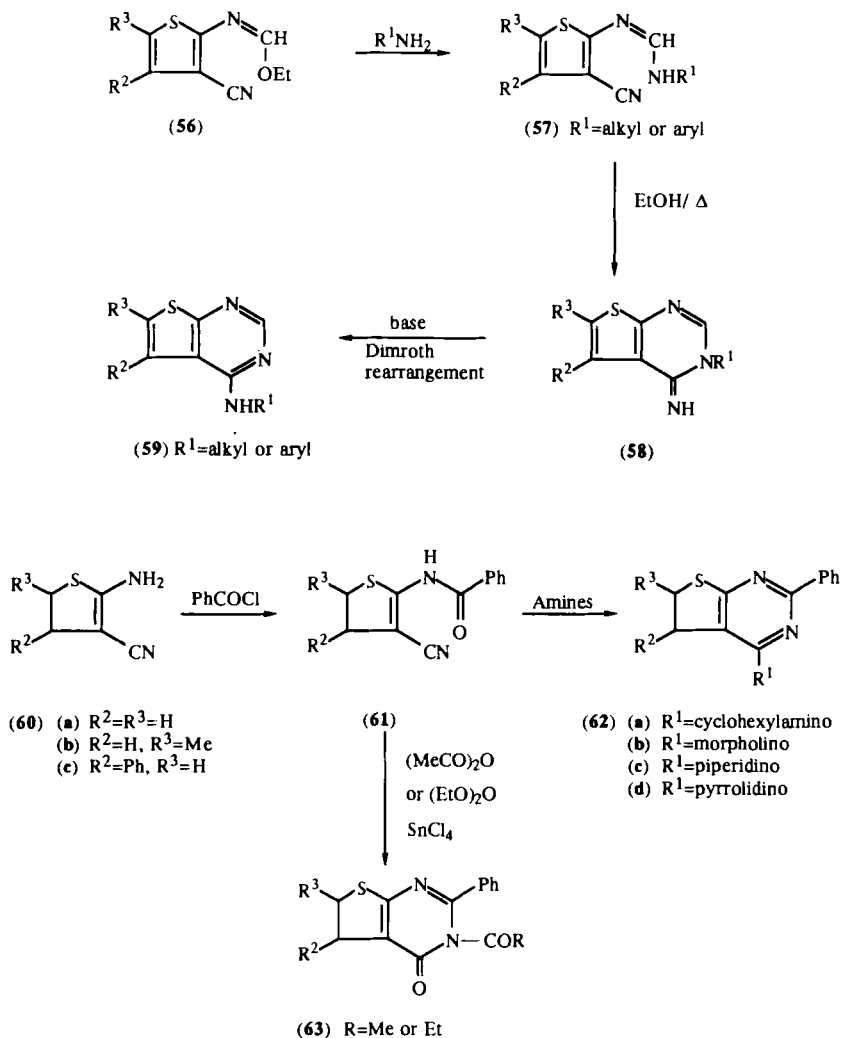


fonylacetonitrile, and 4-chlorophenylsulfonylacetonitrile, the 2-cyano-, 3-cyano-, or 4-cyanopyridines were also used. Reaction of each of these with *o*-aminocarbonitrile **52** gave a mixture of the corresponding 2-substituted 4-chloro- and 4-aminothieno[2,3-*d*]pyrimidines **54a-k** and **55a-k** in varying proportions. A mechanism to explain these results is given in Refs. (83TL4611; 90JHC119).



Heating *o*-aminocarbonitriles **48** with triethyl orthoformate gave 2-ethoxymethyleneaminothiophene-3-carbonitriles **56**, which were refluxed in ethanol containing a primary alkyl or aryl amine to afford the iminoethers **57**. Heating the latter in refluxing ethanol induced cyclization to 4-iminothieno[2,3-*d*]pyrimidines **58**, which rearrange in base to 4-substituted aminothieno[2,3-*d*]pyrimidines **59**. The substituent at position 2 of these thienopyrimidines can vary depending on the initial orthoformate (84EUP103114; 91EUP447891, 91EUP452002).

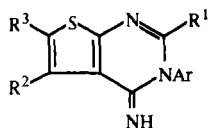
Starting from 2-amino-3-cyano-4,5-dihydrothiophenes **60** the derived 2-benzamido derivatives **61** were treated with cyclohexylamine, morpholine, piperidine, or pyrrolidine to yield the respective 5,6-dihydro-2-phenyl 4-substituted aminothieno[2,3-*d*]pyrimidines **62a-d** (83CPB401). In the presence of tin(IV) chloride, benzamides **61** reacted with acetic (or propionic) anhydride to give the corresponding 3-acetyl(or propionyl)thieno[2,3-*d*]pyrimidin-4-(3*H*)-ones **63** (94LA993).



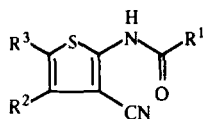
A direct approach to 3-aryl-2-chloro-4-iminothieno[2,3-*d*]pyrimidines **65a** from *N*-aryl isocyanide dichlorides and *o*-aminocarbonitriles **48** was devised by Shishoo and Jain (92JHC883). 3-Aryl-4-imino-2-methylthieno[2,3-*d*]pyrimidines **65b** were obtained by heating a mixture of 2-acetylaminothiophene-3-carbonitriles **64a**, phosphorus pentoxide, a primary arylamine hydrochloride, and *N,N*-dimethylcyclohexylamine hydrochloride in a molar ratio 1 : 6 : 4 : 4, at 160°C (88CS195; 91EUP452002). Following similar reaction conditions but adding 8 parts of water to this reaction mixture

was best for obtaining 3-aryl-2-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **66a** (89CS261).

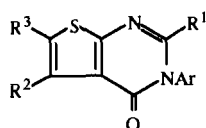
When *o*-aminocarbonitriles **48** ( $R^2 = R^3 = \text{Me}$ ) or **52** were reacted with *N*-arylcyanamides in the presence of dry hydrogen chloride gas followed by aqueous workup, a mixture of 2-amino-3-aryl-4-iminothieno[2,3-*d*]pyrimidines **65d** and the corresponding thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **66b** was isolated. The formation of the latter as a minor product for each derivative was rationalized to proceed via the guanidine intermediate **67**, which hydrolyzed through a Ritter-type reaction and then cyclized during workup (93JHC435).



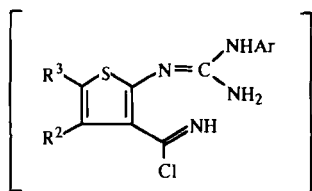
- (65) (a)  $R^1 = \text{Cl}$ ,  $R^2, R^3 = \text{Me}$  or  $(\text{CH}_2)_4$   
 $\text{Ar} = 4\text{-ClC}_6\text{H}_4$  or  $4\text{-BrC}_6\text{H}_4$   
 (b)  $R^1 = \text{Me}$   
 (c)  $R^1 = \text{SMe}$   
 (d)  $R^1 = \text{NH}_2$ ,  $R^2 = R^3 = \text{Me}$  or  $(\text{CH}_2)_4$



- (64) (a)  $R^1 = \text{Me}$   
 (b)  $R^1 = \text{Me}$ ,  $R^2 = \text{Me}$   
 $R^3 = \text{CO}_2\text{Et}$   
 (c)  $R^1 = \text{Ph}$ ,  $R^2 = \text{NH}_2$   
 $R^3 = \text{PhCO}$   
 (d)  $R^1 = \text{CH}_2\text{OMe}$   
 $R^2 = \text{Me}$ ,  $R^3 = \text{CO}_2\text{Et}$



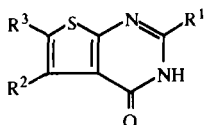
- (66) (a)  $R^1 = \text{Me}$   
 (b)  $R^1 = \text{NH}_2$ ,  $R^2, R^3 = \text{Me}$  or  $(\text{CH}_2)_4$   
 (c)  $R^1 = \text{Cl}$   
 (d)  $R^1 = \text{diethanolamine}$ ,  
 $\text{diethylamine}$ ,  
 $4\text{-methyl-1-piperazinyl}$ ,  
 $\text{morpholino}$ ,  
 $\text{piperidino}$  or  
 $1\text{-pyrrolidinyl}$



- (67)  $R^2, R^3 = \text{Me}$  or  $(\text{CH}_2)_4$

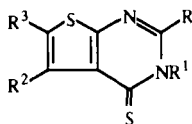
2-Unsubstituted thienopyrimidin-4(3*H*)-one **68a** was obtained by heating *o*-aminocarbonitrile **48**, ( $R^2 = \text{Me}$ ,  $R^3 = \text{CO}_2\text{Et}$ ) in 85% acetic acid containing sodium acetate (92MI3). 2-Methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one **68b** and the 2-phenyl derivative **68c** were formed by heating the corresponding acetamide **64b** (83MI2) and benzamide **64c** (92MI2) in ethanolic hydrochloric acid solution. The methoxyacetamide **64d**, however,

required heating in PPA at 150°C to cyclize into 2-methoxymethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one **68d** (92MI3).



- (**68**) (a)  $R^1 = H$ ,  $R^2 = Me$ ,  $R^3 = CO_2Et$   
 (b)  $R^1 = R^2 = Me$ ,  $R^3 = CO_2Et$   
 (c)  $R^1 = Ph$ ,  $R^2 = NH_2$ ,  $R^3 = PhCO$   
 (d)  $R^1 = CH_2OMe$ ,  $R^2 = Me$ ,  $R^3 = CO_2Et$

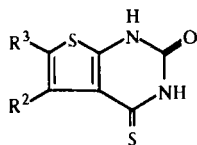
Heating the *o*-aminocarbonitrile **48** ( $R^2 = Ph$ ,  $R^3 = Ac$ ) and triethyl orthoformate yielded the corresponding imine **56**, which was treated with an alcoholic solution of sodium hydrogen sulfide to afford thieno[2,3-*d*]pyrimidine-4(3*H*)-thione **69a** (88JPR585).



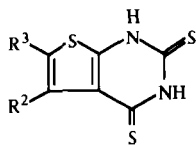
- (**69**) (a)  $R = R^1 = H$ ,  $R^2 = Ph$ ,  
 $R^3 = Ac$   
 (b)  $R = H$ , alkyl or aryl  
 $R^1 = H$ , alkyl, allyl,  
 $NH_2$  or  $OH$

Hernandez *et al.* (81JOC3941) proposed a mechanism to explain the reaction of *o*-aminocarbonitriles **48** ( $R^2, R^3 = H$ ;  $R^2 = Me$ ,  $R^3 = H$ ) and carbonyl sulfide which gave the respective thieno[2,3-*d*]pyrimidin-2(1*H*)-one-4(3*H*)-thiones **70a** and **b**. Abdelrazek and Ead (88JPR585) reported that thiophene **48** ( $R^2 = Ph$ ,  $R^3 = Ac$ ) cyclized in refluxing carbon disulfide to give thieno[2,3-*d*]pyrimidine-2(1*H*),4(3*H*)-dithiones **71a**. However, Gewald *et al.* (91JPR229) found that carbon disulfide reacts with thiophenes **48** [ $R^1 = R^2 = H, Me, (CH_2)_4$ ] in refluxing pyridine to form a mixture of the corresponding dithiones **71b–d** and the tetracyclic dithieno[2,3-*d*]pyrimidine-7-thiones **72a–c**.

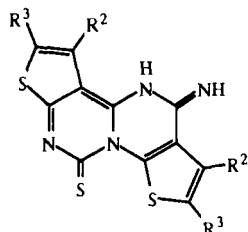
When *o*-aminocarbonitrile **60** was heated with methyl or phenyl isocyanate in methanolic sodium methoxide, the corresponding 3-methyl- or phenylthieno[2,3-*d*]pyrimidin-2-ones **73a,b** formed (85CB4473).



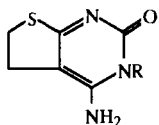
(70) (a)  $R^2=R^3=H$   
(b)  $R^2=Me$ ,  $R^3=H$



(71) (a)  $R^2=Ph$ ,  $R^3=Ac$   
(b)  $R^2=R^3=H$   
(c)  $R^2=R^3=Me$   
(d)  $R^2$ ,  $R^3=(CH_2)_4$

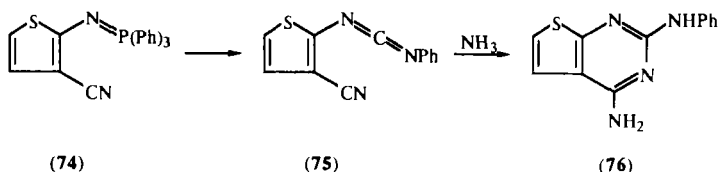


(72) (a)  $R^2=R^3=H$   
(b)  $R^2=R^3=Me$   
(c)  $R^2$ ,  $R^3=(CH_2)_4$



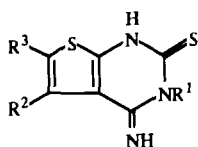
(73) (a)  $R=Me$   
(b)  $R=Ph$

Phenyl isocyanate was used differently by Taylor and Patel (91JHC1857), who synthesized 2-anilinothieno[2,3-*d*]pyrimidine **76** by the sequence of reactions **48**  $\rightarrow$  **74**  $\rightarrow$  **75**  $\rightarrow$  **76**. This synthesis involves (i) adding the *o*-aminocarbonitrile **48** ( $R^2 = R^3 = H$ ) to a mixture of triphenylphosphine and bromine at  $0^\circ C$  to give iminophosphorane **74**, (ii) an aza-Wittig reaction on the iminophosphorane with phenyl isocyanate to yield carbodiimide **75**, and (iii) cyclization of the latter with ammonia.

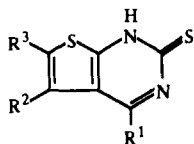


Sukumaran and Rajasakharan [89IJC(B)642] reported that reaction of *o*-aminocarbonitriles **48** and powdered sodium hydroxide in DMF with alkyl or aryl isothiocyanates gave directly 3-alkyl- or 3-aryl-4-iminothieno[2,3-*d*]pyrimidine-2-thiones **77a**. By altering these reaction conditions slightly, the same authors claimed to isolate thioureas **79a**, which were cyclized in boiling pyridine to 4-phenyl- or 4-arylthieno[2,3-*d*]pyrimidine-2(1*H*)-thiones **78a** via Dimroth-type rearrangement of intermediate 4-

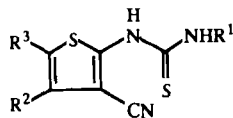
imines [90IJC(B)1070]. Ibrahiem and Tammam (89MI2) obtained thiourea **79b** by allowing *o*-aminocarbonitrile **48** [ $R^2 = R^3 = (CH_2)_4$ ] and phenyl isothiocyanate to react in dioxane. Thiourea **79b** was cyclized to thieno[2,3-*d*]-pyrimidinethione **78b** as above.



(77) (a)  $R^1 = \text{alkyl or aryl}$   
(b)  $R^1 = \text{Ph or Ar}$   
 $R^2, R^3 = (CH_2)_4$

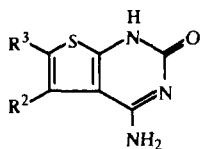


(78) (a)  $R^1 = \text{Ph or Ar}$   
(b)  $R^1 = \text{Ph}, R^2, R^3 = (CH_2)_4$

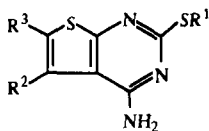


(79) (a)  $R^1 = \text{Ph or Ar}$   
(b)  $R^1 = \text{Ph}, R^2, R^3 = (CH_2)_4$   
(c)  $R^1 = \text{PhCO}$

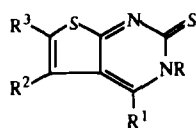
The reaction of *o*-aminocarbonitriles **48** with benzoyl isothiocyanate gave different products depending on reaction conditions. Thioureido **79c** intermediates were isolated by reacting *o*-aminocarbonitriles **48** with benzoyl isothiocyanate in acetone at room temperature. The intermediates **79c** were warmed in dilute sodium hydroxide, and then either acidified to yield 4-aminothieno[2,3-*d*]pyrimidine-2(1*H*)-thiones **80**, or treated with various alkyl halides to afford 2-alkylthio derivatives **81** (89AP322; 91GEP287503). The 3-benzoylthieno[2,3-*d*]pyrimidine-2-thione **82a** was isolated by heating *o*-aminocarbonitrile **48** ( $R^2 = \text{Ph}, R^3 = \text{Ac}$ ) and benzoyl isothiocyanate in acetone (92PS93).



(80)

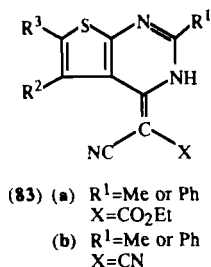


(81)  $R^1 = \text{alkyl}$



(82) (a)  $R = \text{COPh}, R^1 = \text{NH}_2$   
 $R^2 = \text{Ph}, R^3 = \text{Ac}$   
(b)  $R = \text{NH}_2 \text{ or alkyl}$   
 $R^1 = \text{Ph}, R^2, R^3 = (CH_2)_4$

Yamagata *et al.* (86CPB516) found that condensation of 2-acetamido(or benzamido)-4,5-dihydrothiophene 3-carbonitriles **61** ( $R = \text{Me or Ph}$ ) with ethyl cyanoacetate in the presence of sodium hydride afforded ethyl  $\alpha$ -cyano-4-[2-(methyl or phenyl)thienopyrimidine]acetates **83a**. Thiophenes **61** ( $R = \text{Me or Ph}$ ) also reacted with malononitrile in a similar way, to yield the corresponding malononitriles **83b**.

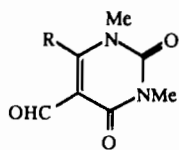


## 2. From Pyrimidines

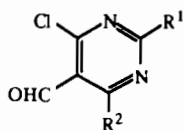
Syntheses of thieno[2,3-*d*]pyrimidines from pyrimidines can be grouped according to the type of substitution on the 5 and 6 positions of the pyrimidine ring.

a. *From 4-Chloropyrimidine-5-carbaldehydes, 5-Acetyl-4-chloropyrimidines, 5-Acetyl-4-mercaptopyrimidines, 4-Chloropyrimidine-5-carbonitriles, or 4-Chloro-5-(phenyl or trimethylsilylethynyl)pyrimidines.* When 4-chloropyrimidine-5-carbaldehydes or -5-carbonitriles were used as starting materials for the synthesis of thieno[2,3-*d*]pyrimidines, a S—C fragment from an alkyl 2-mercaptoacetate or 2-mercaptoacetamide was required for ring closure. Reaction of pyrimidine **84a** with ethyl or methyl 2-mercaptoacetate in dioxane at room temperature in the presence of triethylamine gave the alkoxycarbonylmethylthio intermediate **84b**. Displacement of both chlorine atoms of pyrimidine **85a** to give intermediate **88** required heating with methyl 2-mercaptoacetate in pyridine at 90°C. Heating **84b** in ethanolic sodium ethoxide and **88** in toluene containing triethylamine provided 5-unsubstituted thienopyrimidines **89a** (90JHC717) and **90a** (93JHC1065), respectively. Direct synthesis of these thienopyrimidines was also reported using elevated temperatures. In a Russian patent (83URP725433) the ethyl analog of the ester **90a** was prepared. Thirteen 4-(amino or substituted amino)-6-chloropyrimidine-5-carbaldehydes **85b** were converted into the corresponding thieno[2,3-*d*]pyrimidines **90b** by heating in methanol containing methyl 2-mercaptoacetate and triethylamine (93JHC1065). 5-Methylthieno[2,3-*d*]pyrimidines **92** were obtained directly from the reaction of 5-acetyl-4-chloropyrimidines **91a** with ethyl 2-mercaptoacetate in the presence of base (90JIC327; 91PHA26) or from 5-acetyl-4-mercaptopyrimidine **91b** with ethylbromoacetate in the presence of base (91PJS4).

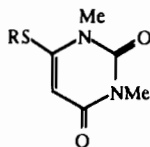
Heating 4-chloropyrimidine-5-carbonitriles **87** or **93** and alkyl 2-mercaptoacetates in ethanol containing base gave directly 5-aminothieno[2,3-*d*]pyrimidines **89** (88JHC959, 88KGS1559; 89JPR893, 89JPR957) or **94**



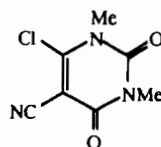
(84) (a)  $R=Cl$   
(b)  $R=SCH_2CO_2Et$



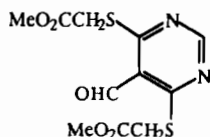
(85) (a)  $R^1=H, R^2=Cl$   
(b)  $R^1=H$  or  $NH_2$ ,  
 $R^2=NH_2, NRR', NHA_r$



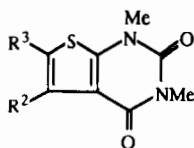
(86) (a)  $R=CH_2CO_2Et$   
(b)  $R=H$



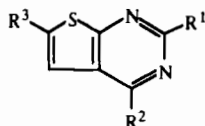
(87)



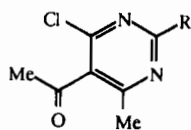
(88)



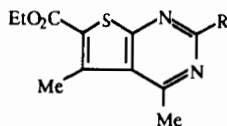
(89) (a)  $R^2=H, R^3=CO_2Et$   
(b)  $R^2=NH_2, R^3=CO_2Et$   
(c)  $R^2=R^3=H$   
(d)  $R^2=H, R^3=Br, NO_2$   
or  $CHO$



(90) (a)  $R^1=H, R^2=SCH_2CO_2Me$   
 $R^3=CO_2Me$   
(b)  $R^1=H$  or  $NH_2, R^2=NH_2$ ,  
 $NRR', NArR, R^3=CO_2Me$   
(c)  $R^1=R^2=R^3=Me$



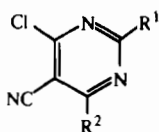
(91)



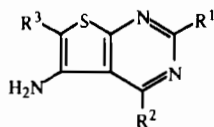
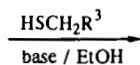
(92)

$R=Ph$  or  $4-ClC_6H_4$

(90JHC717), respectively. Intermediate 4-alkylthiopyrimidine-5-carbonitriles were isolated first when the reaction was carried out at room temperature (87KGS1131; 88KGS1559, 88LA633; 91OPP413; 93JHC1065).



(93)

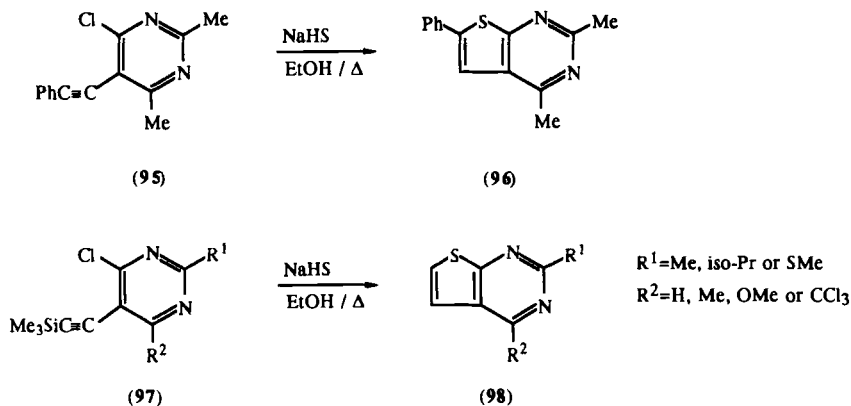


(94)

$R^3=CO_2Me, CO_2Et$ ,  
 $CONH_2, Ac$  or  $CN$

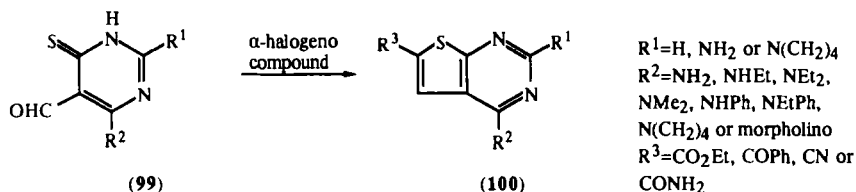
Sakamoto *et al.* (82CPB2417) synthesized 4,6-dimethyl-2-phenylthieno[2,3-*d*]pyrimidine **96** by reacting 4-chloro-2,6-dimethyl-5-phenylethynylpyrimidine **95** with sodium hydrosulfide in boiling ethanol. In a similar manner, 4-chloro-5-(trimethylsilylethynyl)pyrimidines **97** were converted into thieno[2,3-*d*]pyrimidines **98** (86CPB2719; 89YZ642).





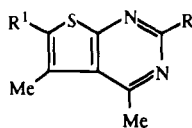
b. *From 5-Acetyl- or 5-Formylpyrimidin-4-(3H)-thiones.* Hirota *et al.* (90JHC717) reacted 1,3-dimethyl-6-mercaptopuracil **86b** with chloroacetaldehyde in the presence of sodium acetate and obtained thieno[2,3-*d*]-pyrimidine **89c**.

A large number of 5-unsubstituted thieno[2,3-*d*]pyrimidines **100** were obtained by reacting 5-formylpyrimidine-4(3*H*)-thiones **99** with the appropriate  $\alpha$ -halogeno compound (ethyl bromoacetate, phenacyl bromide, chloroacetonitrile or chloroacetamide) in aqueous sodium carbonate at 50°C (93JHC1065).

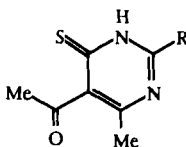


When 5-acetylpyrimidine-4(3*H*)-thiones **101** are cyclocondensed with  $\alpha$ -halogeno compounds, 5-methylthieno[2,3-*d*]pyrimidines **102** are obtained. The isolation of *S*-alkyl intermediates in these synthesis was sometimes unpredictable.

5-Acetyl-6-methyl-phenylpyrimidine-4(3*H*)-thione **101** reacts with phenacyl bromide or chloroacetamide in aqueous sodium carbonate or with chloroacetic acid in refluxing glacial acetic acid to give the corresponding 6-substituted thieno[2,3-*d*]pyrimidines **102a** (88PHA537; 90MI6). Compound **101a** ( $R = \text{Ph}$ ) was also reacted with acrylonitrile to give the intermediate **103a**, which cyclized and oxidized in sulfuric acid containing potassium permanganate to afford the 7,7-dioxide **104a** (91PHA26). El-

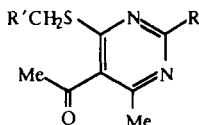


- (101) (a) R=Ph or p-ClC<sub>6</sub>H<sub>4</sub>  
 (b) R=naphthyl  
 (c) R=Ar  
 (d) R=CH=CHAr

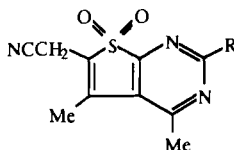


- (102) (a) R=COPh, CONH<sub>2</sub> or CO<sub>2</sub>H  
 (b) R=naphthyl, R¹=Me, Et or NHPPh  
 (c) R=Ar or CH=CHAr

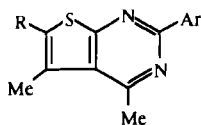
Farargy *et al.* (91PJS4) *S*-alkylated 2-naphthylpyrimidine-4(3*H*)-thione **101b** with bromoacetone, ethyl bromoacetate, and bromoacetanilide, isolating the intermediates **103b** which were cyclodehydrated by heating in base to give the 2-naphthylthieno[2,3-*d*]pyrimidines **102b**. When 2-arylpyrimidine-4(3*H*)-thiones **101c** (89MI, 89MI5; 90JIC327, 90PHA792; 92MI4) or 2-arylvinylpyrimidines **101d** (89MI4, 89PHA348) reacted with activated  $\alpha$ -halomethylene compounds in base, a great variety of 2-(aryl or arylvinyl)-4,5-dimethyl-6-substituted thieno[2,3-*d*]pyrimidines **102c** were obtained. Two 7,7-dioxo derivatives **104** were synthesized from the appropriate pyrimidines **101d** (90CCC1049) in a manner analogous to the preparation of **104**.



- (103) (a) R=Ph, R'=CH<sub>2</sub>CN  
 (b) R=naphthyl, R'=COMe, CO<sub>2</sub>Et or CONHPPh  
 (c) R=Ar, R'=CO<sub>2</sub>Et  
 (d) R=Ar, R'=CONHNH<sub>2</sub>  
 (e) R=Ph, R'=CO<sub>2</sub>H

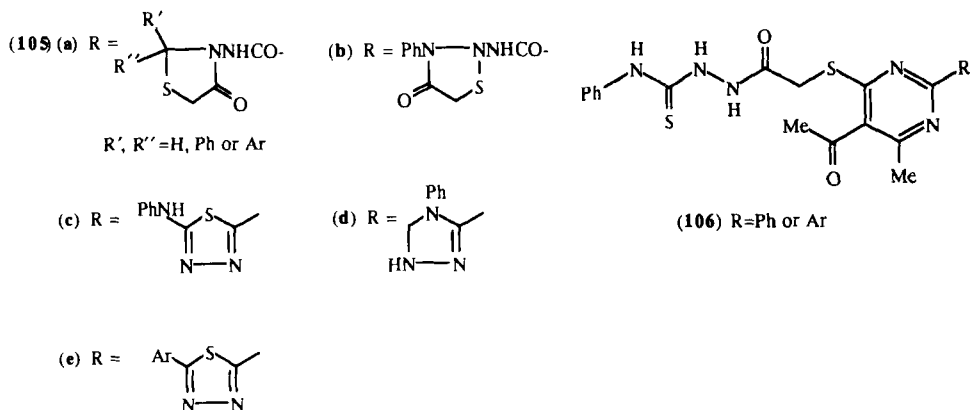


- (104) (a) R=Ph  
 (b) R=CH=CHAr, Ar=Ph or 4-ClC<sub>6</sub>H<sub>4</sub>

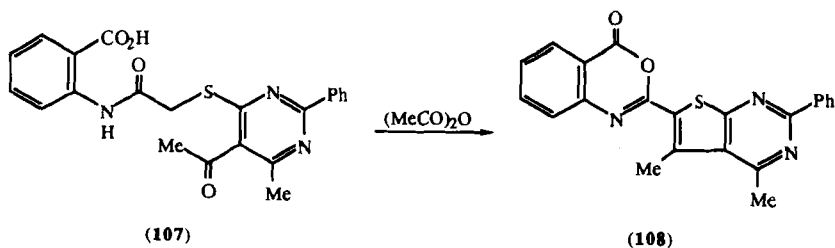


El-Bahaie *et al.* (88JIC695) synthesized thiazolidinothieno[2,3-*d*]pyrimidine derivatives **105a** by a three-step reaction sequence starting from pyrimidines **103**. These compounds were converted into the acid hydrazides **103** by heating with hydrazine hydrate in ethanol. The acid hydrazides **103d**

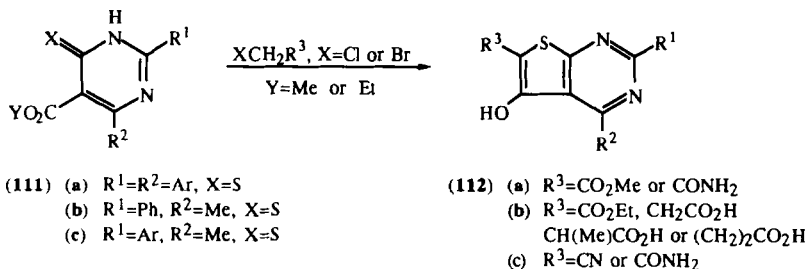
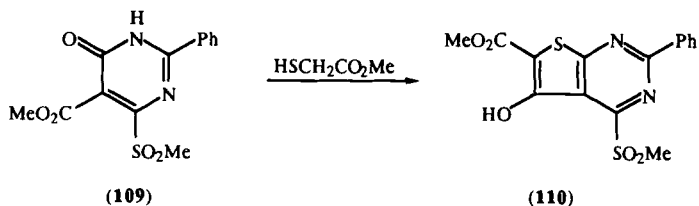
were then condensed with aromatic aldehydes or ketones to give hydrazones, which were then cyclocondensed with 2-mercaptoacetic acid to give directly the thiazolidino derivatives **105a**. Further derivatives of compound **105a** were synthesized by the same authors one year later (89MI1). One slight modification of this route involved reacting the acid hydrazides **103d** with phenyl isothiocyanate to give *N*-phenylhydrazine carbothioamides **106**, which were treated with chloroacetyl chloride to afford thiazolidinothieno[2,3-*d*]pyrimidines **105b**. When heated with orthophosphonic acid at 120°C, *N*-phenylhydrazine carbothioamides **106** gave the 1,3,4-thiadiazolo-thienopyrimidine **105c**; but when **106** are heated with dilute sodium hydroxide, the 1,2,4-triazolo derivative **105d** is the result (90MI4). On the other hand, heating hydrazones derived from **103** and aromatic aldehydes with acetic acid containing sodium acetate afforded the oxadiazolothieno[2,3-*d*]pyrimidines **105e** (89PHA492; 90MI4).



Later, El-Bahaie *et al.* (91MI2, 91PJC1059) used the readily available acid **103**, converting it to the corresponding acid chloride which was, in turn, reacted with anthranilic acid to yield the anthranil **107**. Treatment of compound **107** with acetic anhydride produced a benzoxazinythieno[2,3-*d*]pyrimidine **108**.

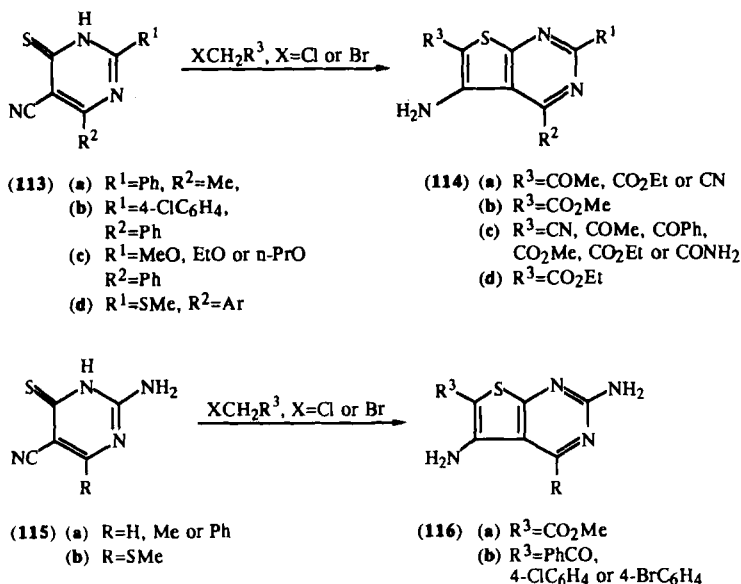


From 4-(*Oxo or thioxo*)pyrimidine-5-carboxylates, 4-Thioxopyrimidine-5-carbonitriles, or 5-Allylpyrimidine-4(3*H*)-thiones. Kohra *et al.* (88JHC959) cyclized the oxopyrimidinecarboxylate **109** with methyl 2-mercaptoacetate in the presence of triethylamine in methanol and obtained the 5-hydroxythieno[2,3-*d*]pyrimidine **110**. The 6-substituent of 5-hydroxythieno[2,3-*d*]pyrimidines **112** was varied by cyclocondensing 4-thioxopyrimidine-5-carboxylates with alkylating agents in methanol or ethanol containing sodium methoxide or triethylamine. Thus, pyrimidines **111a** were treated with methyl chloroacetate or chloroacetamide; pyrimidine **111b** with ethyl bromoacetate, chloroacetic acid, and  $\alpha$ - or  $\beta$ -bromopropionic acids; and pyrimidine **111c** with chloroacetonitrile or acetamide, whereupon each pyrimidine was converted into the corresponding thieno[2,3-*d*]pyrimidine **112a** (88GEP258012), **112b** (89MI3), and **112c** (90MI10).



Similar cyclocondensations between 4-thioxopyrimidine-5-carbonitriles **113** or **115** and alkylating agents provided a large number of 5-aminothieno[2,3-*d*]pyrimidines **114** or **116**. 2-Phenyl-6-methylpyrimidines **113** were reacted with chloroacetone, ethyl bromoacetate, or chloroacetonitrile to give the appropriate thieno[2,3-*d*]pyrimidines **114** [88JCR(S)46; 90PHA216; 93PHA667]. 2-(4-Chlorophenyl)-6-phenylpyrimidine **113** gave the thieno[2,3-*d*]pyrimidine **114** upon treatment with methyl chloroacetate [84JCS(P1)2447], whereas the 2-alkoxy derivatives **113** were reacted with a variety of  $\alpha$ -halomethylene compounds to afford thieno[2,3-*d*]pyrimidines **114** (89GEP273441). Several 2-aryl-2-methylthiopyrimidines **113d** were cyclocondensed with ethyl bromoacetate to afford thieno[2,3-*d*]pyrimidines

**114d** (89MI3). 2-Aminopyrimidines **115a** and **115b** were treated respectively with methyl chloroacetate and various phenacyl bromides to afford the corresponding thieno[2,3-*d*]pyrimidines **116a** and **116b** (83S402; 87KGS1377).

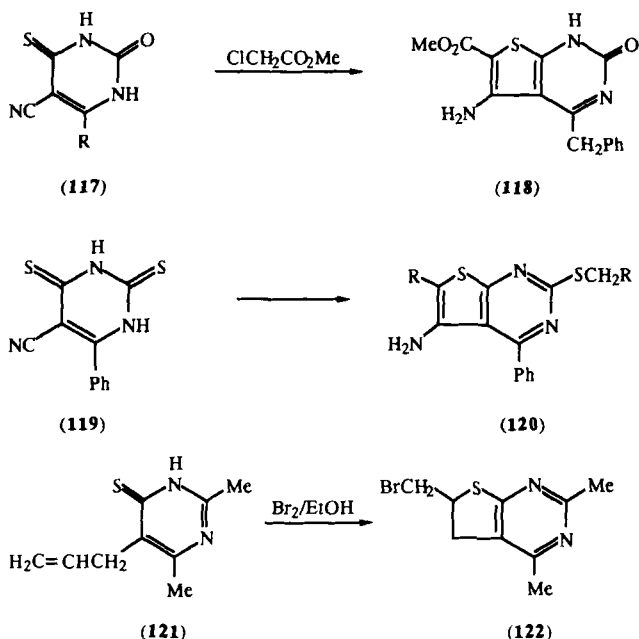


The reaction of 2-oxo-4-thioxypyrimidin-5-carbonitrile **117** with methyl chloroacetate in the presence of methanolic sodium ethoxide gave thieno[2,3-*d*]pyrimidine **118** [84JCS(P1)2447]. 2,4-Dithioxypyrimidine-5-carbonitrile **119** was reacted with acetonitrile or various  $\alpha$ -chlorocarbonyl compounds in ethanol containing sodium acetate to give the corresponding thieno[2,3-*d*]pyrimidines **120** (91PS223).

Russian workers (82KGS118) reported the synthesis of 5,6-dihydrothieno[2,3-*d*]pyrimidine **122** by brominating 5-allylpyrimidine-4(3*H*)-thione **121**.

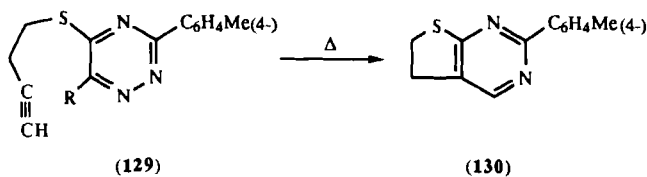
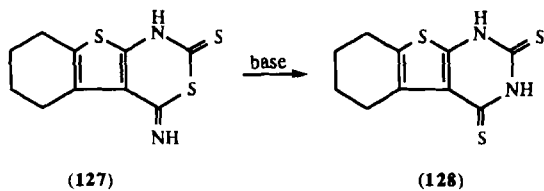
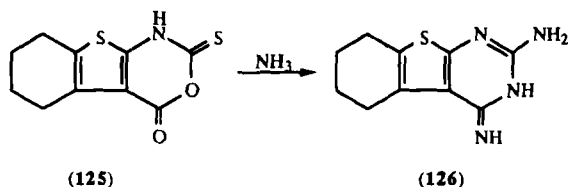
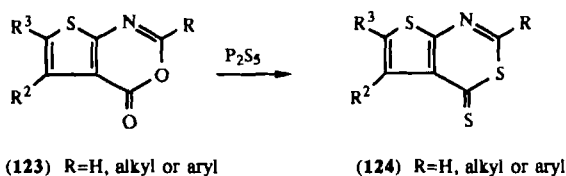
### 3. Miscellaneous Syntheses

Thieno[2,3-*d*]pyrimidines can also be synthesized by cyclic transformations from other ring systems. Thieno[2,3-*d*]oxazin-4-ones **123** were transformed into 3-substituted thieno[2,3-*d*]pyrimidin-4-ones **19a-d** by treat-



ment with hydrazine hydrate, hydroxylamine hydrochloride or primary amines [81JAP(K)53681, 81JAP(K)59778, 81JAP(K)56389, 81JIC(B)982; 87JAP(K)132884]. Ibraheim *et al.* (89MI2) reacted the tetrahydrobenzothieno[2,3-*d*]oxazine-2(1*H*)-thione **125** with ammonia and obtained the 2-amino-4-iminothieno[2,3-*d*]pyrimidine **126** (89MI2). Leistner *et al.* (86GEP234677, 86PHA96) converted thieno[2,3-*d*]oxazin-4-ones **123** into the corresponding thienothiazine-4-thiones **124** by heating in xylene with phosphorus pentasulfide; then these investigators treated the latter with hydrazine hydrate, hydroxylamine hydrochloride, or primary amines and obtained thieno[2,3-*d*]pyrimidine-4-thiones **69b**. When Sukumaran and Rajasekharan [89IJC(B)642] refluxed 4-iminobenzothienothiazine-2(1*H*)-thione **127** in ethanol in the presence of base, it rearranged to the known benzothienopyrimidine-2(1*H*),4(3*H*)-dithione **128**. Heating compound **127** with aniline and various arylamines at 80°C caused its isomerization to 4-imino-3-(phenyl or aryl)benzothieno[2,3-*d*]pyrimidine-2(1*H*)-thiones **77b**.

Taylor and Pont (87JOC4287) heated 5-(3-butylnylthio)-1,2,3-triazines **129** in 1,3,5-triisopropylbenzene at 232–236°C and caused a cycloaddition across the N-2/C-5 positions of the triazine ring to give, after loss of MeCN or PhCN, 5,6-dihydrothieno[2,3-*d*]pyrimidine **130**.



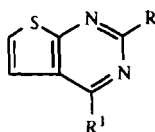
## B. REACTIONS

### 1. Oxidation and Reduction

Oxidation of 6-formylthienopyrimidinedione **89d** ( $R^3 = \text{CHO}$ ) with Jones' reagent converted the aldehyde group to a carboxylic acid group. Hydrogenation of **89d** ( $R^3 = \text{CHO}$ ) with palladium(II) oxide as catalyst at  $100^\circ\text{C}$  reduced the aldehyde group to a methyl group.

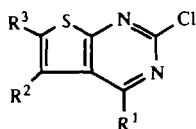
The 4-methyl group of **131** was oxidized to an aldehyde group with selenium dioxide in dioxane (89YZ642). The cyano derivative **112c** ( $R^3 = \text{CN}$ ) was oxidized to the amide **112c** ( $R^3 = \text{CONH}_2$ ) with 30% hydrogen peroxide in methanolic sodium hydroxide (90MI10).

2-Chloro- and 2,4-dichlorothienopyrimidines **132a** and **b** were reduced at the C-4/N-3 double bond by sodium borohydride in a chloroform-ethanol

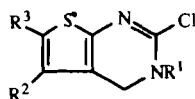


(131)

mixture at 50°C to give the corresponding 2-chloro-3,4-dihydrothieno[2,3-*d*]pyrimidines **133a** [80EUP8408; 81JAP(K)104870, 81JHC67, 81JMC376; 82JAP(K)77687].



- (132) (a)  $R^1 = H$   
 (b)  $R^1 = Cl$   
 (c)  $R^1 = Ar$   
 (d)  $R^1 = amino$   
 (e)  $R^1 = morpholino$   
 $R^2, R^3 = (CH_2)_4$



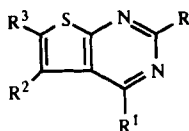
- (133) (a)  $R^1 = H$   
 (b)  $R^1 = CH_2CO_2R$   
 $R = alkyl \text{ or } aryl$

## 2. Ring Chlorination and Subsequent Nucleophilic Substitution

In three patents [81JAP(K)110678; 85EUP150469; 94JAP(K)16557] the substitution of the chlorine atoms of 2-chloro-4-arylthieno[2,3-*d*]pyrimidines **132** by a variety of cyclic diamines was described. Pathak *et al.* [91IJC(B)618] reacted 2-chloro-3-phenylthieno-pyrimidin-4-ones **66c** with various secondary amines and obtained the respective 2-amino derivatives **66d**. Boehm *et al.* (85GEP226893; 86PHA23), Fukumi *et al.* (83EUP82023), and Brown *et al.* (90EUP404356) treated 2,4-dichlorothieno[2,3-*d*]pyrimidines **132b** with aromatic and aliphatic amines and found that, depending on the conditions and the amine used, the 4-chloro atom can be replaced first to give 2-chloro-4-amino compounds **132d** and then further reacted to give 2,4-diamino compounds **134a**. When 2-chloro-4-morpholino compound **132e** was heated with aniline, the dianilino derivative **134b** was obtained.

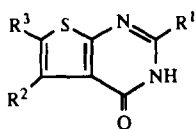
The thienopyrimidin-4(3*H*)-ones **135** were converted into the corresponding 4-chloro derivatives **136** almost exclusively by heating with phosphoryl chloride containing *N,N*-dimethylaniline as catalyst. The 4-chloro compounds **136** were then treated with a variety of aliphatic and aromatic amines to afford the corresponding 4-alkyl or aryl aminothieno



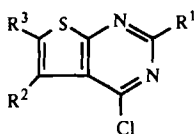


- (134) (a)  $R, R^1 = \text{amino}$ ,  
 $R^2, R^3 = \text{Me or } (\text{CH}_2)_4$   
 (b)  $R = R^1 = \text{anilino}$ ,  
 $R^2, R^3 = (\text{CH}_2)_4$

[2,3-*d*]pyrimidines [81JHC1277, 81SAP822; 82IJC(B)666; 83PHA269, 83URP745160; 85KGS925; 86GEP237663, 86MI1; 87GEP245666, 87GEP245667, 87GEP248593; 89YZ464; 90EUP370704; 91PHA422; 92JHC883, 92PHA20; 93PHA192, 93PHA585].



(135)



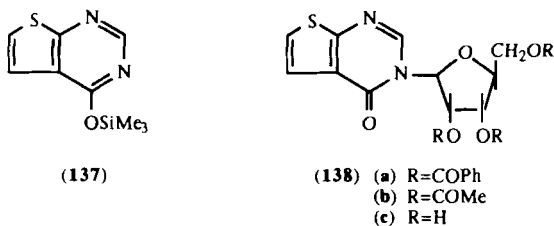
(136)

$R^1 = \text{H, alkyl, aryl}$   
 $\text{amino, N}_3 \text{ or CO}_2\text{R}$   
 $R^2, R^3 = \text{H, alkyl, aryl}$   
 $\text{or CO}_2\text{R}$

### 3. *N*-Alkylation, *N*-Acylation, *O*-Acylation, and *S*-Alkylation

2-Chloro-3,4-dihydrothieno[2,3-*d*]pyrimidines **133a** were alkylated at position 3 with a variety of  $\alpha$ -halogeno carbonyl compounds in the presence of phase-transfer catalysis to give derivatives **133b** [81JAP(K)104870, 81JAP(K)110678]. Compound **2a** ( $R^2 = \text{H}$ ,  $R^3 = \text{Me}$ ) was alkylated at N-3 with ethyl 2-bromopropionate in the presence of sodium hydride (89JOC990). Other derivatives of **2a** were alkylated at N-3 with a variety of alkyl halides, ethyl bromoacetate, or ethyl bromopropionate. The reactions were performed in aqueous sodium hydroxide and dichloromethane or toluene mixtures in the presence of tetrabutylammoniumhydrogen sulfate or tetrabutylammonium bromide (or chloride). Under similar conditions, derivatives **3a** were alkylated at N-1 and N-3 (83PHA135; 86PHA661). Alkylation of derivatives **3b** at N-1 by ethyl bromoacetate was also reported [89MIP1; 90JAP(K)225485; 93MI1]. The 3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl] derivative of **3b** was acetylated and benzoylated at N-1 (89USP835157). Derivative **2f** was alkylated at N-3 with *N*-triphenylmethyl-5-[2-(4-bromomethyl)biphenyl]tetrazole in the presence of sodium hydride in DMF (92EUP502725).

Unsubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-one **2a** was converted into the trimethylsilyl derivative **137** by heating in hexamethyldisilazane. Silyl derivative **137** was alkylated at N-3 with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranose in the presence of stannic chloride in 1,2-dichloroethane or 2,3,5-tri-*O*-acetyl-D-furanosyl bromide in refluxing benzene in the presence of mercuric oxide and mercuric bromide. The intermediate nucleosides **138a,b** obtained were deblocked without isolation to 3- $\beta$ -D-ribofuranosylthieno[2,3-*d*]pyrimidin-4-one **138c** (85JMC423). A similar route has been used for the *N*-1 alkylation of 4-aminothieno[2,3-*d*]pyrimidin-2-one with 1,2,3,5-tetra-*O*-acetyl- $\beta$ -D-ribofuranose [80JCS(P1)1853].



5-Aminothienopyrimidines **94** were monoacetylated or diacetylated by reaction with acetyl chloride and triethylamine or acetic anhydride, respectively (88LA633).

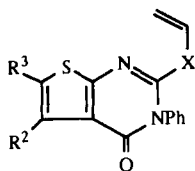
3-Hydroxythieno[2,3-*d*]pyrimidines **19d** were acylated at the N—OH group with acyl chlorides, acid anhydrides, or isocyanates [81JAP(K)8389, 81JAP(K)53681, 81JAP(K)56389, 81JAP(K)59778].

Alkylation of thieno[2,3-*d*]pyrimidin-4-one-2-thiones **4a** and **4b** with chloroacetic acid in base followed by acidification yielded the corresponding 2-carboxymethylthio derivatives [81IJC(B)538; 87PHA160]. Various alkyl halides and dimethyl sulfate were employed for the *S*-alkylation of compounds **4a** and **4b** in the presence of base [86GEP240892; 89IJC(B)642; 90MI2, 90PHA493, 90PHA827; 92MI1]. *S*-Alkylation of compound **4d** by chloroacetanilide derivatives and of compound **17** with bromoacetophenone derivatives has also been reported (93MI2; 94PHA64).

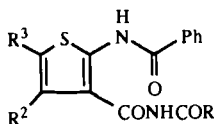
The 3-phenylthieno[2,3-*d*]pyrimidine-2,4-diones **3b** and the corresponding -4-one-2-thiones **4b** were converted into the respective 2-allyloxy **139a** and 2-allylthio **139b** derivatives by reaction with allyl chloride in base (89KGS347).

#### 4. Electrophilic Substitution

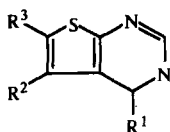
4-Aminothienopyrimidines **81** were reacted under Vilsmeier conditions to give the corresponding 4-dimethylaminomethyleneamino derivatives



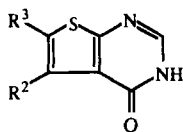
(139) (a) X=O  
(b) X=S



(140) R=Me or Et



(141) (a) R<sup>1</sup>=Cl or MeO  
R<sup>2</sup>=Me, R<sup>3</sup>=H  
(b) R<sup>1</sup>=Cl or MeO  
R<sup>2</sup>=CHBr<sub>2</sub>, R<sup>3</sup>=H  
(c) R<sup>1</sup>=MeO, R<sup>2</sup>=H,  
R<sup>3</sup>=Me  
(d) R<sup>1</sup>=MeO, R<sup>2</sup>=H  
R<sup>3</sup>=CH<sub>2</sub>Br or CHBr<sub>2</sub>



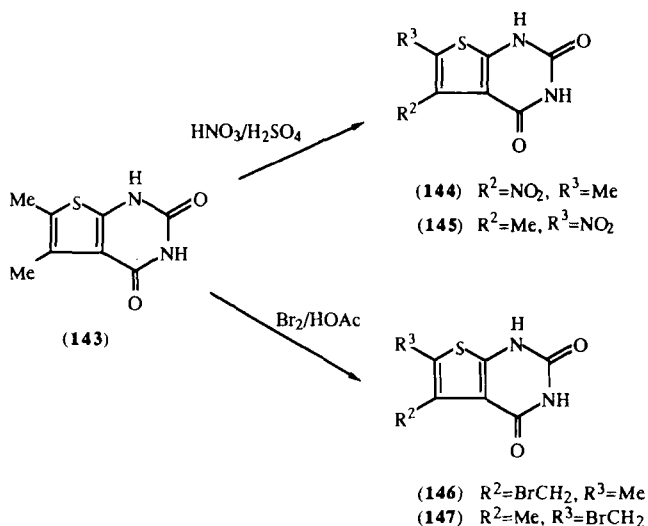
(142) (a) R<sup>2</sup>=CHBr<sub>2</sub>, R<sup>3</sup>=H  
(b) R<sup>2</sup>=Me, R<sup>3</sup>=Br  
(c) R<sup>2</sup>=Br, R<sup>3</sup>=Me

(91PHA457). Thieno[2,3-*d*]pyrimidine **89c** was brominated, nitrated, and formylated at position 6 to give the 6-bromo, 6-nitro, and 6-formyl derivatives **89d**, respectively (90JHC717).

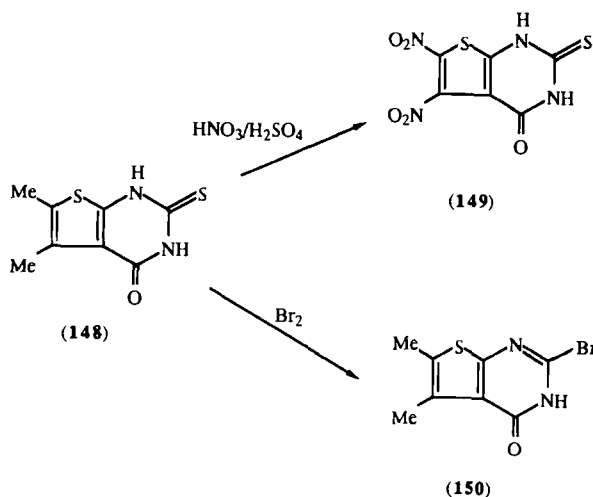
Bromination of compounds **141a** with carbon tetrachloride and *N*-bromosuccinimide in the presence of benzoyl peroxide took place at the methyl group to give the corresponding dibromomethyl derivatives **141b**. When the same reaction conditions were applied to compound **141c**, the result was a mixture of the corresponding bromomethyl and dibromomethyl derivatives **141d**. Using bromine in carbon tetrachloride on compounds **141a** afforded the dibromomethyl derivative **142a**. In a more polar solvent such as DMF, bromine caused electrophilic substitution at position 6 of compounds **141a** and position 5 of compound **141c** to give the corresponding bromo derivatives **142b** and **142c** (87KFZ197).

Nitration at position 5 of thieno[2,3-*d*]pyrimidines **90a** and **90** (R<sup>1</sup> = H, R<sup>2</sup> = NMe<sub>2</sub>, R<sup>3</sup> = CO<sub>2</sub>Me) occurs readily with nitric acid in sulfuric acid. However, the methoxycarbonylmethylthio group of compound **90a** is hydrolyzed in the process (93JHC1065). Nitration of 5,6-dimethylthieno[2,3-*d*]pyrimidinedione **143** using nitric acid in sulfuric acid gave a mixture of the 5-nitro **144** and 6-nitro **145** compounds.

Under the same reaction conditions 5,6-dimethylthienopyrimidin-4(3*H*)-one-2(1*H*)-thione **148** afforded the corresponding 5,6-dinitro product **149**. Compound **143** was also brominated using bromine in acetic acid to give



a mixture of 5-bromomethyl **146** and 6-bromomethyl **147** derivatives. On the other hand, bromination of thione **148** with bromine water gave 2-bromo-5,6-dimethylthienopyrimidin-4(3H)-one **150** (93KGS1574).



### 5. Miscellaneous Reactions

The ester group directly attached to position 6 of the thieno[2,3-d]-pyrimidine ring was hydrolyzed to a carboxylic acid group by heating with

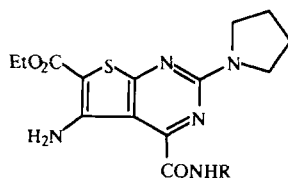
dilute sodium hydroxide (93JHC1065). The alkoxycarbonylmethyl groups of compounds **51a,b** were hydrolyzed and decarboxylated when heated with dilute hydrochloric acid or were converted into amides (83CPB1177). Thieno[2,3-*d*]pyrimidin-4-ones **63** are unstable to acidic conditions. Column chromatography of these compounds on silica gel caused ring opening to give *N*-acylthiophene-3-carboxamides **140** (94LA993). The 4-methoxycarbonylmethylthio group of **94** ( $R^1 = H$ ,  $R^2 = SCH_2CO_2Me$ ,  $R^3 = CO_2Me$ ) was displaced by ethoxide or methoxide ions by heating in ethanolic or methanolic solutions. The reaction with ethoxide also caused transesterification of the 6-methoxycarbonyl group (93JHC1065). Konno *et al.* (89YZ46, 89YZ642) reacted 2,4-dimethylthieno[2,3-*d*]pyrimidine **98** ( $R^1 = R^2 = Me$ ) with benzaldehyde in acetic anhydride and obtained the 4-styryl compound exclusively. Similar region selectivity of two methyl groups of **98** ( $R^1 = R^2 = Me$ ) was observed on nitrosation in acidic conditions, on bromination with bromine in chloroform, or on chlorination with phosphoryl chloride and phosphorus pentachloride, which converted the 4-methyl group into oxime, bromomethyl, and trichloromethyl, respectively.

The 4-trichloromethyl compound **98** ( $R^1 = Me$ ,  $R^2 = CCl_3$ ) reacted with triphenyl phosphine to give the respective iminophosphoranes, which underwent Wittig reactions with benzaldehyde and crotonaldehyde (89YZ642). The trichloromethyl group of compounds **2c** was converted into a trimethyl orthoester group by refluxing in methanolic sodium methoxide and then hydrolyzed with dilute aqueous acid to a methoxycarbonyl group. On the other hand, the 2-trichloromethyl moiety in compound **49d**, when refluxed in ethanol, methanol, or dioxane containing hydrazine hydrate, afforded the corresponding 2-ethoxy, 2-methoxy, or 2-hydrazino derivatives **49** (89ZN488).

2-Chloromethyl compounds **2d** were converted into the 2-styryl derivatives **49h** in two steps: first by reacting with triphenylphosphine in refluxing toluene, and then by condensing the resulting triphenylphosphonium chloride with benzaldehyde in methanol containing 10% aqueous sodium carbonate (85JHC825). The 2-chloromethyl group of **2d** was either acetylated with potassium acetate in acetic acid or hydrolyzed in aqueous sodium carbonate (90AF567).

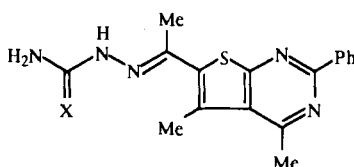
The 5-amino group of compound **114a** ( $R^3 = CN$ ) was transformed into an oxalamidic ethyl ester group with ethyl oxalyl chloride (93PHA667). Condensation of 4-amino-5,6,7,8-tetrahydrobenzo derivative **49a** with ethylethoxymethylenemalonate or ethylethoxymethylenecyanoacetate afforded the corresponding 4-amino acrylates (90MI5).

The 6-ethoxycarbonyl group of compound **94** ( $R^1 = \text{pyrrolidino}$ ,  $R^2 = R^3 = CO_2Et$ ) was unaffected during reaction with ammonia solution or *n*-propanolamine, giving instead the corresponding amides **151a,b** (88LA633).

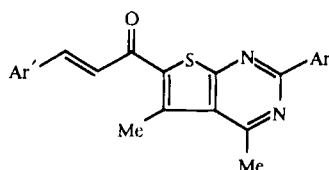


(151) (a)  $R = \text{NH}_2$   
(b)  $R = n\text{-C}_3\text{H}_7$

Condensation of the 6-acetyl group of thieno[2,3-*d*]pyrimidines **102c** ( $R = \text{Ph}$ ,  $R^1 = \text{COMe}$ ) with semicarbazide or thiosemicarbazide gave the respective hydrazones **152a,b**; but in the presence of aqueous sodium hydroxide and an aromatic aldehyde, the  $\alpha,\beta$ -unsaturated derivatives **153** were obtained (89MI5).

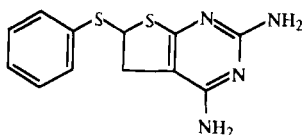


(152) (a)  $X = \text{O}$   
(b)  $X = \text{S}$



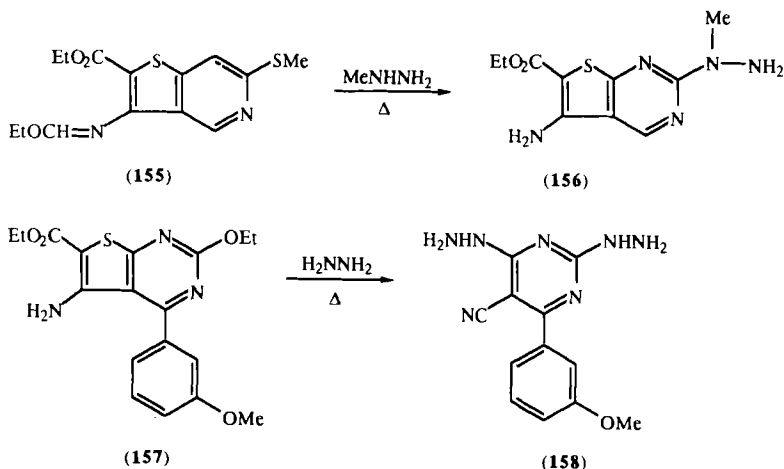
(153)

Reaction of the thieno[2,3-*d*]pyrimidinedithione **71b** with ammonia solution gave 2,4-diaminothiopyrimidine **131b**. This compound was treated with *sec*-BuLi and then with 3-trifluoromethylbenzenesulfonyl chloride to give, after acidic workup, the 6-(3-trifluoromethylphenylthio)thienopyrimidine **154** (90HCA797).

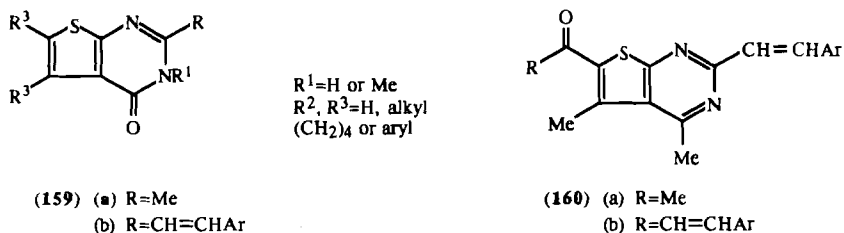


(154)

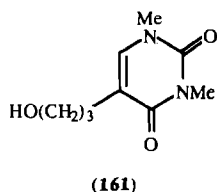
Heating thieno[2,3-*d*]pyrimidine **155** with excess methylhydrazine at reflux temperature caused hydrazinolysis of the 5-ethoxymethyleneamino group and substitution of the methylthio group to give the hydrazine derivative **156**. The latter underwent condensation with *p*-nitrobenzaldehyde to give the corresponding hydrazone (94JPR160). Treating thieno[2,3-*d*]pyrimidine **157** with hydrazine hydrate gave the unexpected ring-opened product **158** (89JPR957).



When 2-methylthieno[2,3-*d*]pyrimidin-4-ones **159a** were heated with aromatic aldehydes at  $180^\circ\text{C}$  in the presence of zinc chloride, the 4-oxo-2-(2-arylvinyl)thieno[2,3-*d*]pyrimidines **159b** were formed (85GEP225993). 2-(2-Arylvinyl)-6-acetylthieno[2,3-*d*]pyrimidines **160a** reacted with aromatic aldehydes in the presence of sodium hydroxide to yield the condensation product **160b** (89PHA348).

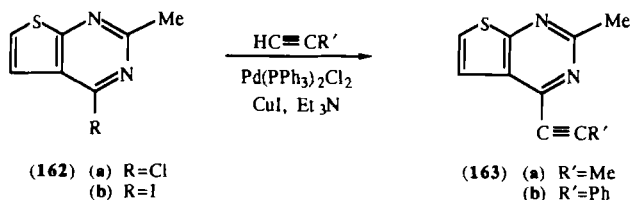


Hydrogenation of **89d** ( $\text{R}^3 = \text{CHO}$ ) using Raney nickel under 50 atm induced desulfurization to give 5-(3-hydroxypropyl)-1,3-dimethyluracil **161** (90JHC717).



The 4-methyl group of 2,4-dimethylthieno[2,3-*d*]pyrimidine **98** ( $\text{R}^1 = \text{R}^2 = \text{Me}$ ) was converted into a bromomethyl group by reaction with bro-

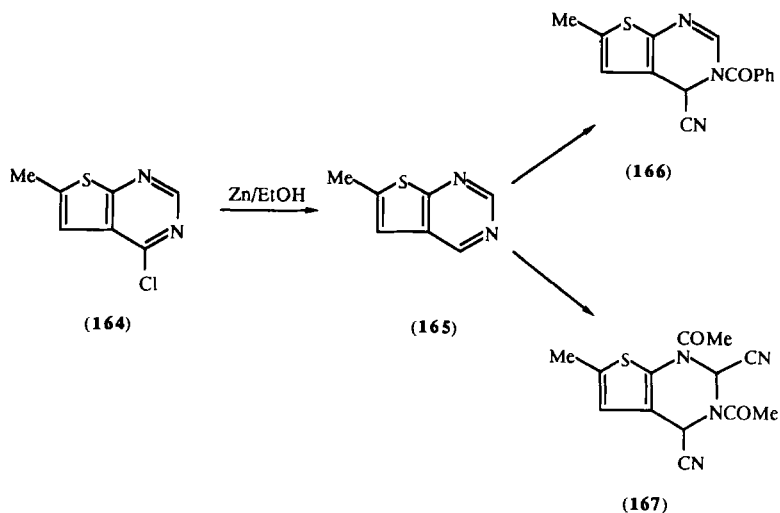
mine in chloroform. The 4-chloro compound **162a** was transformed into the 4-iodo compound **162b** by reaction with sodium iodide and hydrogen iodide in methyl ethyl ketone. The latter was coupled with propyne or phenylacetylene in the presence of bis(triphenylphosphine)palladium(II) chloride and cuprous iodide in triethylamine to afford the corresponding 4-(1-propynyl) **163a** and 4-phenylethynyl **163b** derivatives (89YZ642).



Deamination of 3-amino derivative **23** with sodium nitrile in acetic acid gave 5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one [85IJC(B)432]. Using the same reaction procedure, 3-amino derivative **82b** ( $\text{R} = \text{NH}_2$ ) was converted into the thieno[2,3-*d*]pyrimidine-2(1*H*)-thione **78b** (90JHC269).

Dehydrobromination of the 6-bromomethyl derivative **122** by refluxing in a methanolic solution of sodium methoxide gave 2,4,6-trimethylthieno[2,3-*d*]pyrimidine (82KGS118).

Dechlorination of 4-chloro-6-methylthieno[2,3-*d*]pyrimidine **164** with zinc in ethanol and acetic acid at 80°C gave compound **165**. The latter was subjected to the Reissert reaction using two equivalents each of tributyltin cyanide and acyl chloride in dichloromethane at room temperature. With benzoyl chloride the mono-Reissert adduct **166** was obtained, whereas with acetyl chloride the di-Reissert product **167** (86JHC545).

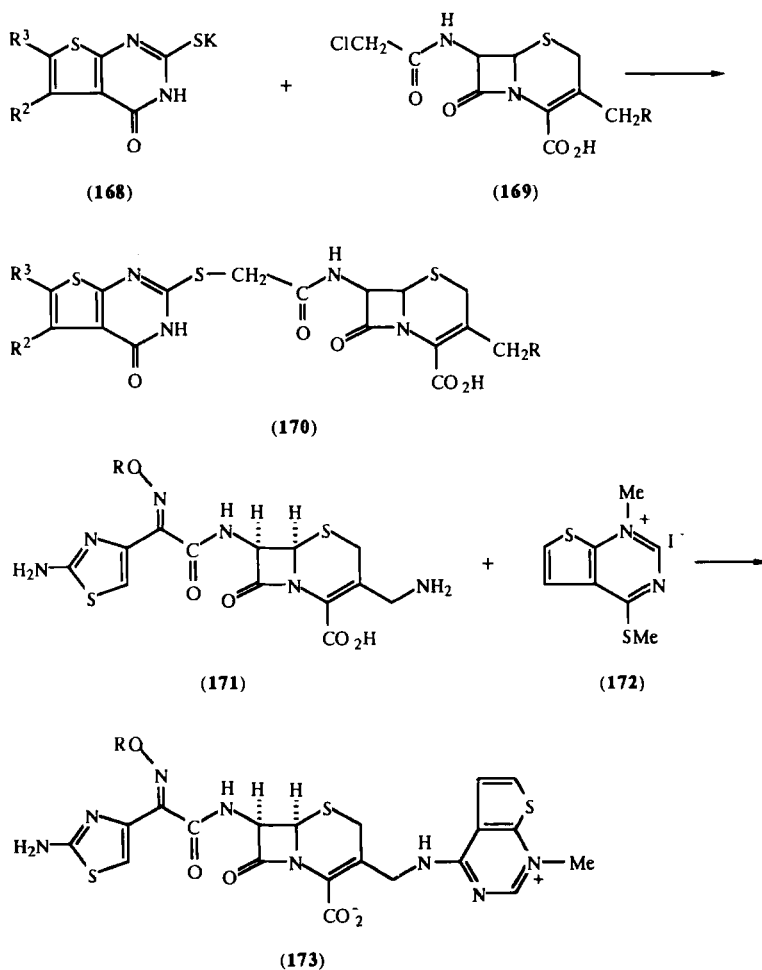




Thieno[2,3-*d*]pyrimidines have also been used during the preparation of cephalosporin derivatives (88EUP253507).

Complexes of thieno[2,3-*d*]pyrimidines **100** ( $R^1 = \text{NH}_2$ ;  $R^2 = \text{NHEt}$ ,  $\text{NEt}_2$ ,  $\text{NEtPh}$ , or morpholino;  $R^3 = \text{CO}_2\text{Me}$ ) with copper(II), nickel(II), and cobalt(II) have been obtained. The metals were found to coordinate with N-1 of the thieno[2,3-*d*]pyrimidines (88MI2; 94MI4).

7 $\beta$ -(Thienopyrimidyl-2-thioacetamido)cephalosporanic acid derivatives **170** were prepared by reaction of the appropriate 7 $\beta$ -chloroacetamidocephalosporanic acids **169** with the thieno[2,3-*d*]pyrimidine potassium salts **168** (87PHA160). The 4-methylthio group of quaternized thieno[2,3-*d*]pyrimidine **172** was displaced by the 3-aminomethyl group of cephalosporins **171** to afford cephalosporin derivatives **173** (89AUP584898).



## C. PHYSICOCHEMICAL PROPERTIES

For the thieno[2,3-*d*]pyrimidines the following spectral data are available.

**UV data:** 81CS135, 81JHC43, 81JOC3941; 82IJC(B)666; 84JCS(P1)2447 85JMC423; 86CPB516; 88JHC959; 89AP322; 90JPR223; 93JHC435.

**IR data:** 81CS135, 81IJC(B)538, 81JHC43; 82IJC(B)666; 83CPB1177, 83PHA135, 83S402; 84JCS(P1)2447, 84JHC375; 85CB4473, 85KGS925, 85S190; 86CPB516, 86JHC545; 87JOC4287; 87KG1377; 88CS195, 88JCR(S)46, 88JHC959, 88JPR585, 88KGS1559, 88LA633, 88PHA537; 89AP322, 89CPB2122, 89CS261, 89IJC(B)642, 89JOC990, 89PHA492, 89YZ642, 89ZN488; 90HCA797, 90IJC(B)1070, 90JHC119, 90JHC269, 90MI6, 90PHA827; 91JHC1857, 91PHA457; 92JHC883, 92MI2, 92MI3; 93JHC435, 93JHC1065; 94JPR160.

**<sup>1</sup>H-NMR data:** 81CS135, 81IJC(B)538; 82CPB2417; 83CPB401, 83CPB1177, 83IJC(B)76, 83PHA135, 83S402; 84JCS(P1)2447, 84JHC375; 85CB4473, 85JMC423, 85S190; 86CPB516, 86CPB2719, 86JHC545; 87JHC581, 87KGS1131, 87KGS1377; 88CS195, 88JCR(S)46, 88JHC959, 88JPR585, 88KGS1559, 88LA633, 88PHA537; 89CPB2122, 89CS261, 89IJC(B)642, 89JOC990, 89MI1, 89PHA492, 89YZ642, 89ZN488; 90HCA797, 90IJC(B)1070, 90JHC119, 90JHC269, 90JHC717, 90MI6; 90PHA827; 91JHC1857, 91MI2, 91OPP413, 91PHA457; 92JHC883, 92MI2, 92MI3; 93JHC435, 93JHC1065; 94JPR160.

**<sup>13</sup>C-NMR data:** 86JHC545; 88CS195; 89CS261, 89JOC990; 91JPR229.

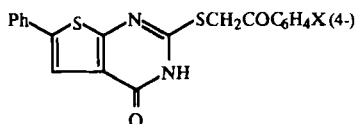
**Mass spectral data:** 82KGS118; 83CPB1177; 84JHC375; 85JHC889; 88JCR(S)46; 89CS261; 90HCA797, 90JHC119; 92JHC883; 93JHC435.

## D. APPLICATIONS

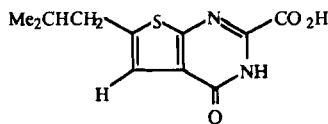
The following biological properties of thieno[2,3-*d*]pyrimidines have been patented: acaricidal (81SAP822; 84EUP103114), aldose reductase inhibitory [89MIP1; 90JAP(K)225485], angiotensin II receptor blocking (93MIP1), antiallergic (85EUP144101; 87EUP234557), antibiotic (83URP745160; 88EUP253507) antidepressant [89USP835157; 94JAP(K)16557], antihypertensive (89USP835157; 92EUP502725), anti-ulcer (85EUP144101), bactericidal (89AUP584898; 90EUP370704), blood platelet aggregation inhibitory [82JAP(K)77687; 83EUP82023; 85GEP226893], fungicidal [81JAP(K)8389, 81JAP(K)53681, 81JAP(K)59778; 91GEP293824], herbicidal (91EUP447891); hypersensitivity inhibitory (83GEP231103), insecticidal (84EUP103114; 90EUP356158; 91EUP447891), and immunomodulatory and oncostatic (89MIP2).

4-Oxothieno[2,3-*d*]pyrimidine carboxylates **174** were among the several different structural classes of compounds that inhibit rat lens and human

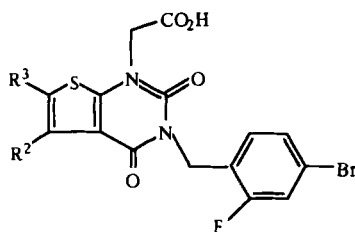
placental aldose reductase. Detailed structure-activity relations at the molecular and electronic levels have been described (82MI1). Thieno[2,3-*d*]pyrimidinediones **176a-d** showed potent aldose reductase inhibitory activity with  $IC_{50}S$  in the  $10^{-8}$  *M* range (93MI1).



(174) X=H, Cl, OMe  
or NO<sub>2</sub>



(175)



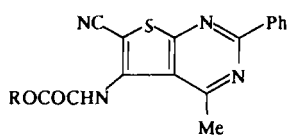
(176) (a) R<sup>2</sup>=R<sup>3</sup>=H  
(b) R<sup>2</sup>=H, R<sup>3</sup>=Me  
(c) R<sup>2</sup>=CH(Me)<sub>2</sub>, R<sup>3</sup>=H  
(d) R<sup>2</sup>=Cl, R<sup>3</sup>=H

Analgesic and antiinflammatory activities superior to that of acetylsalicylic acid were found for thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **2b** (R<sup>1</sup> = Me) and **2a**, respectively (84MI2). 3-Aminothieno[2,3-*d*]pyrimidin-4-ones **19c** (R = Me) and **19c** (R = benzyl) exhibited both effects at levels close to those exhibited by acetylsalicylic acid (88MI1). Similar effects and levels of activity were also found for thienopyrimidin-4(3*H*)-one-2(1*H*)-thiones **4b** (90MI3) and 3-aminothieno[2,3-*d*]pyrimidin-4-ones **174** (94PHA64). Several 2-(*N,N*-disubstituted)amino-3-phenylthieno[2,3-*d*]pyrimidin-4-ones **66d** showed both analgesic and CNS-depressant activity. The analgesic effect was comparable to that of morphine [91IJC(B)618].

The antiallergic tiprinast **175** was found to inhibit cutaneous anaphylaxis in rats, histamine release from the rat peritoneal mast cells, and nasal constriction arising from antigen in rats. Its effects were more potent and longer-acting than the similar effects of disodium cromoglycate (85MI1). Bolus intravenous injection of compound **175** produced a transient vasodepressor response and concurrent bradycardia in closed-chest, anesthetized dogs. The significance of this response, if any, in humans or in relation to

the mechanism of antiallergic action(s) of this compound remains uncertain (87MI1).

The *N*-(thieno[2,3-*d*]pyrimid-5-yl)oxalamidic ethyl ester **177a** and carboxylic acid **177b** exhibited antianaphylactic activity (93PHA667). Compounds **178a–c** inhibited growth in the tobacco callus assay, thereby showing potential as anticytokinins (86MI4).

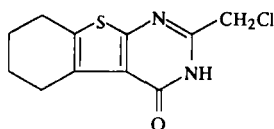


(177) (a) R=OEt  
(b) R=OH



(178) (a) R<sup>2</sup>=H, R<sup>3</sup>=Me  
(b) R<sup>2</sup>=R<sup>3</sup>=H  
(c) R<sup>2</sup>, R<sup>3</sup>=(CH<sub>2</sub>)<sub>4</sub>

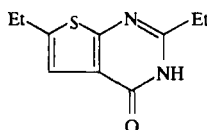
2-Chloromethyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4(3*H*)-one **179** decreased the levels of all types of lipids in hyperlipemic rabbits and of triglycerides in guinea pigs and rats. Furthermore, acute and chronic toxicity studies showed the compound to be safe. It was concluded that compound **179** can be developed as a potential antihyperlipaemic drug (90AF567).



(179)

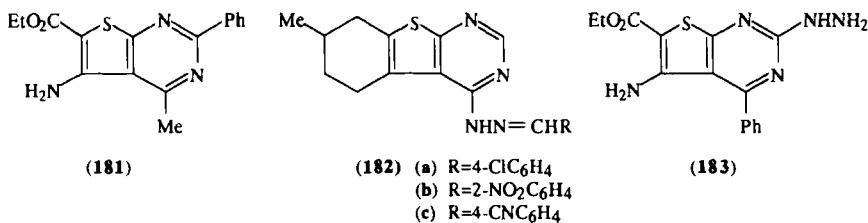
3-β-D-Ribofuranosylthieno[2,3-*d*]pyrimidin-4-one **138c** inhibited the growth of murine L-1210 leukemic cells *in vitro* with an ID<sub>50</sub> of  $3 \times 10^{-5}$  M. From biochemical studies it appeared that the compound may act as an adenosine analog (85JMC423).

Potent antiviral activity was found for 2,6-diethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one **180** (81KFZ40). The antiviral activity of some brominated thieno[2,3-*d*]pyrimidines has also been studied (87KFZ197).

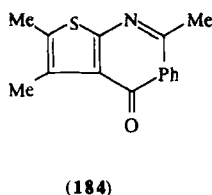


(180)

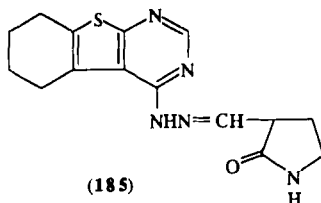
7 $\beta$ -(Thienopyrimid-2-ylthioacetamido)cephalosporanic acids **170** were active against Gram-positive bacteria and inactive in the case of Gram-negative bacteria (87ACC1997). Moderate antimicrobial activity was exhibited by ester **181** against *E. coli*, *B. mycoides*, and *S. cerevisiae* using the disc diffusion method (90PHA216). The antimicrobial activities of tetrahydrobenzothieno[2,3-*d*]pyrimidines **182a-c** have been discussed (91JIC169). The 7,7-dioxide derivative **104a** was tested against *Salmonella* sp. and found to have antibacterial activity comparable to that of penicillin G (91PHA26). Significant antibacterial activity against *S. coccus* and *Serrata* sp. was shown by the 5-amino derivatives **120** (R = CN) and **183** (91PS223).



3-Phenyl-2,5,6-trimethylthienopyrimidin-4-one **184** caused diuretic activity in rats [81JIC(B)982].



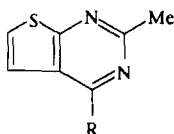
In a study aimed at the treatment of *Pneumocystis carinii* and *Toxoplasma gondii* infections in AIDS patients, several 2,4-diaminothieno[2,3-*d*]pyrimidine analogs **49b** of the potent dihydrofolate reductase inhibitors trimetrexate and piritrexim were tested. Although several compounds



showed this effect, it was not considered large enough to warrant further preclinical evaluation (93JMC3103).

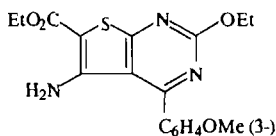
4-(Indolin-2-on-3yl)hydrazino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-pyrimidine **185** showed 10–20% herbicidal activity against pigweed, velvet leaf, red millet, green foxtail, and soya bean (81JHC1277).

Thienopyrimidine **49a**, which exhibited significant inhibition on *Aspergillus parasiticus* growth and aflatoxin (B<sub>1</sub>, B<sub>2</sub>, G<sub>1</sub> and G<sub>2</sub>) production, is considered a potential fungicide and antimycotoxigenic agent (92AP301). Among the large number of 4-alkyl- or arylaminothieno[2,3-*d*]pyrimidines studied, derivatives **186a–c** showed the most effective antifungal action against *Piricularia oxyzae* (89YZ464).



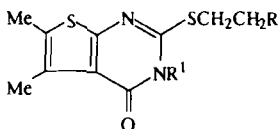
(**186**) (a) R=NHBu  
(b) R=NEt<sub>2</sub>  
(c) R=piperidino

Moderate leishmanicidal activity against amastigotes of *Leishmania donovani* in hamsters was shown by thienopyrimidine **187** (89JPR957).



(**187**)

The tertiary bases of compounds **188a–c** were quaternized with methyl iodide. The resulting quaternary salts displayed spasmolytic activity inhibiting induced contractions in isolated guinea pig ileum (90PHA493).



(**188**) (a) R=NMe<sub>2</sub>, R<sup>1</sup>=Et or Ph  
(b) R=piperidine, R<sup>1</sup>=Et or Ph  
(c) R=morpholine, R<sup>1</sup>=Et or Ph

### III. Thieno[3,2-*d*]pyrimidines

#### A. SYNTHESIS

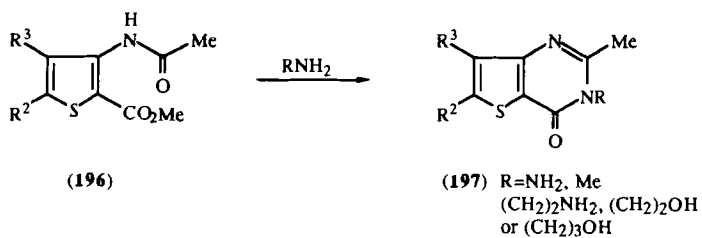
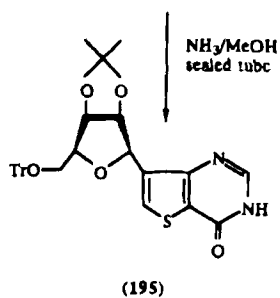
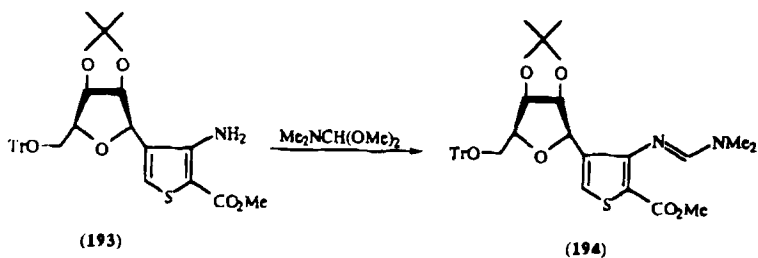
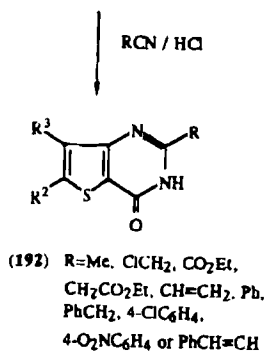
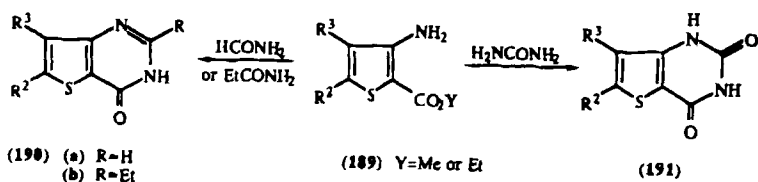
##### 1. From Thiophenes

a. *From Alkyl 3-Aminothiophene-2-carboxylates.* The majority of thieno[3,2-*d*]pyrimidines have been synthesized from alkyl 3-aminothiophene-2-carboxylates **189**. The C—N fragment required for pyrimidine fusion is introduced either directly or stepwise. Therefore, heating *o*-aminoesters **189** with formamide or propionamide gave directly thienopyrimidin-4-(3*H*)-ones **190a,b** (85IZV1858, 88EUP276057; 88USP4725599). By a longer procedure, methyl 3-amino-4-(2',3'-*O*-isopropylidene-5'-*O*-trityl- $\beta$ -D-ribofuranosyl)thiophene-2-carboxylate **193** was reacted first with DMF–dimethyl acetal to afford the dimethylaminomethyleneimine derivative **194**. The latter was then cyclized into the corresponding thienopyrimidinone **195** by heating with saturated methanolic ammonia at 70°C in a sealed vessel (82JOC4633). Reaction of **170** with urea in DMF at 200°C produced the 7-methyl- or 7-arylthienopyrimidine-2(1*H*),4(3*H*)-diones **191** (94JHC305). A large number of 2-substituted thienopyrimidin-4-(3*H*)-ones **192** were prepared through cyclocondensation of *o*-aminoesters **189** (Y = Et) with a variety of nitriles in the presence of dry hydrogen chloride gas [94IJC(B)436].

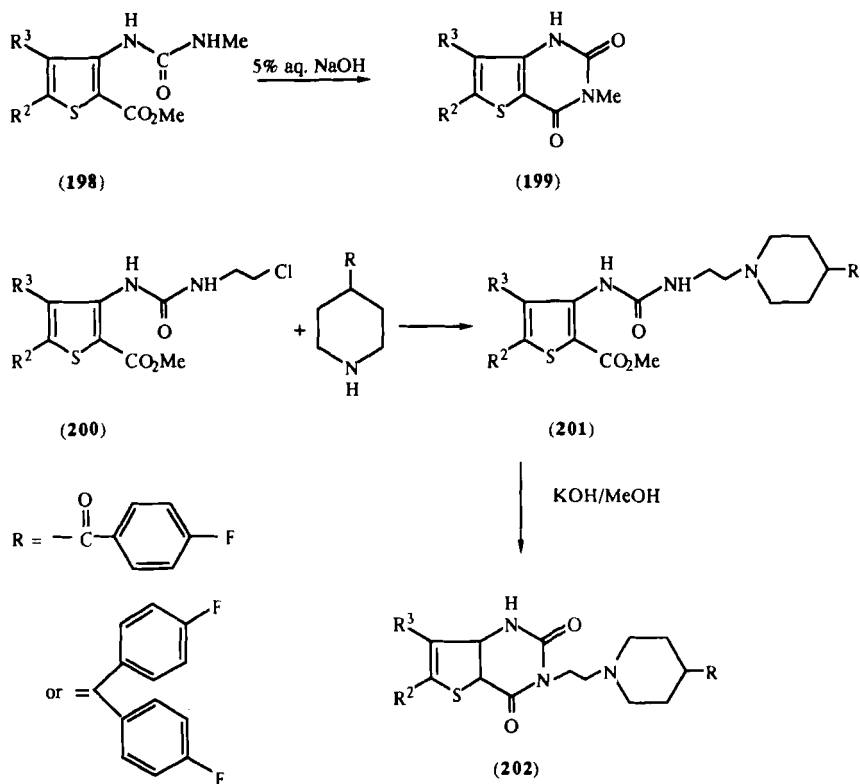
To synthesize 2-methyl-3-substituted thienopyrimidin-4-ones **178**, a two-step reaction was applied. *o*-Aminoesters **189** (Y = Me) were reacted with acetic anhydride in the presence of 4-dimethylaminopyridine to give methyl 3-acetylaminothiophene-2-carboxylates **196**. These were then cyclized by heating with primary amines to the thieno[3,2-*d*]pyrimidin-4-ones **197** (91GEP295381; 92PHA577).

Two approaches were used to synthesize 3-substituted thieno[3,2-*d*]pyrimidine-2,4-diones **199** and **202**. *o*-Aminoesters **189** (Y = Me) could be converted into methylureas **198** by consecutive treatment with phosgene and methylamine. The methylureas **198** were then cyclized into 3-methylthienopyrimidinediones **199** by stirring in DMF containing 5% aqueous sodium hydroxide (89EUP311321). On the other hand, chloroethylureas **200**, derived by treating *o*-aminoesters **189** (Y = Me) were treated with either 4-(4-fluorobenzoyl)piperidine or bis(4-fluorophenyl)methyl-4-piperidylidene to give the corresponding urea derivatives **201**. The latter were ring-closed to the 3-ethyl-substituted aminothienopyrimidinediones **202** by heating in a solution of methanolic potassium hydroxide (91MI1).

3-(4-Bromo-2-fluorobenzyl)benzothienopyrimidine-2(1*H*),3-diones **205** were prepared by refluxing ureas **204** in a methanolic solution of sodium



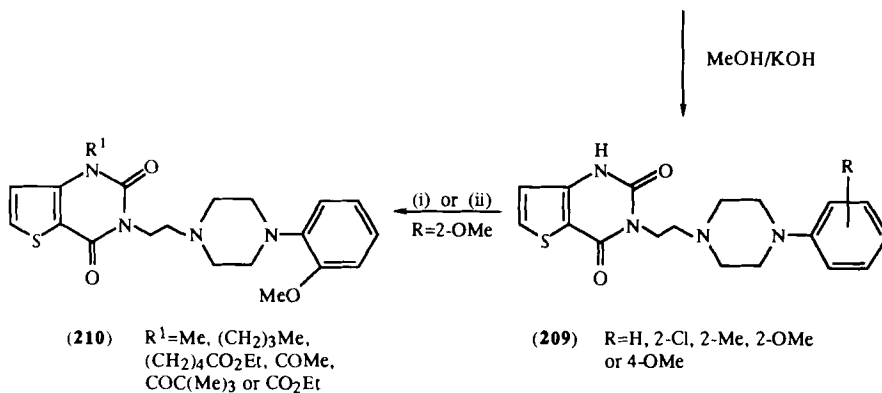
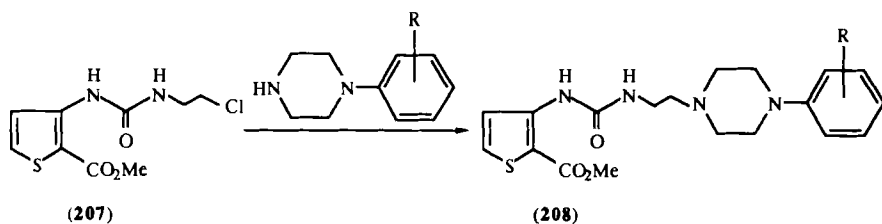
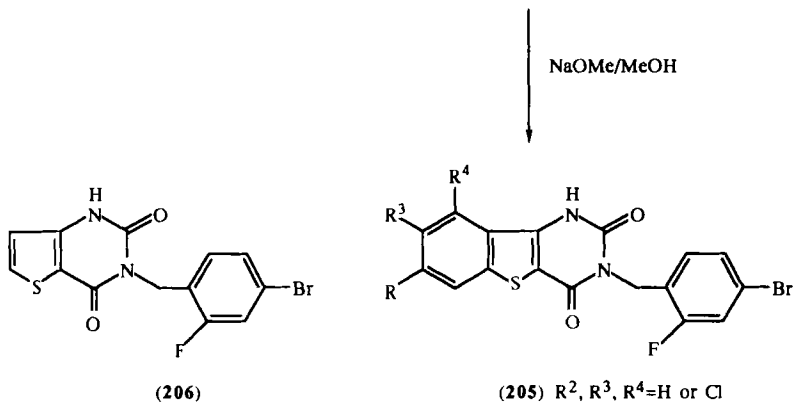
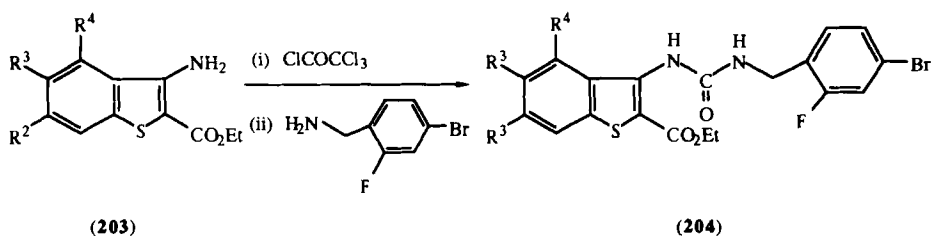




methoxide. Ureas **204** were obtained by heating **203** with trichloroacetyl chloride at 60–70°C followed by cyclization of the resulting trichloroaceta-mido derivative with 4-bromo-2-fluorobenzylamine at room temperature. Following the same procedure, thieno[3,2-*d*]pyrimidinedione **206** was synthesized from *o*-aminoester **189** ( $R^2 = R^3 = \text{H}$ ,  $Y = \text{Et}$ ) (93MI1).

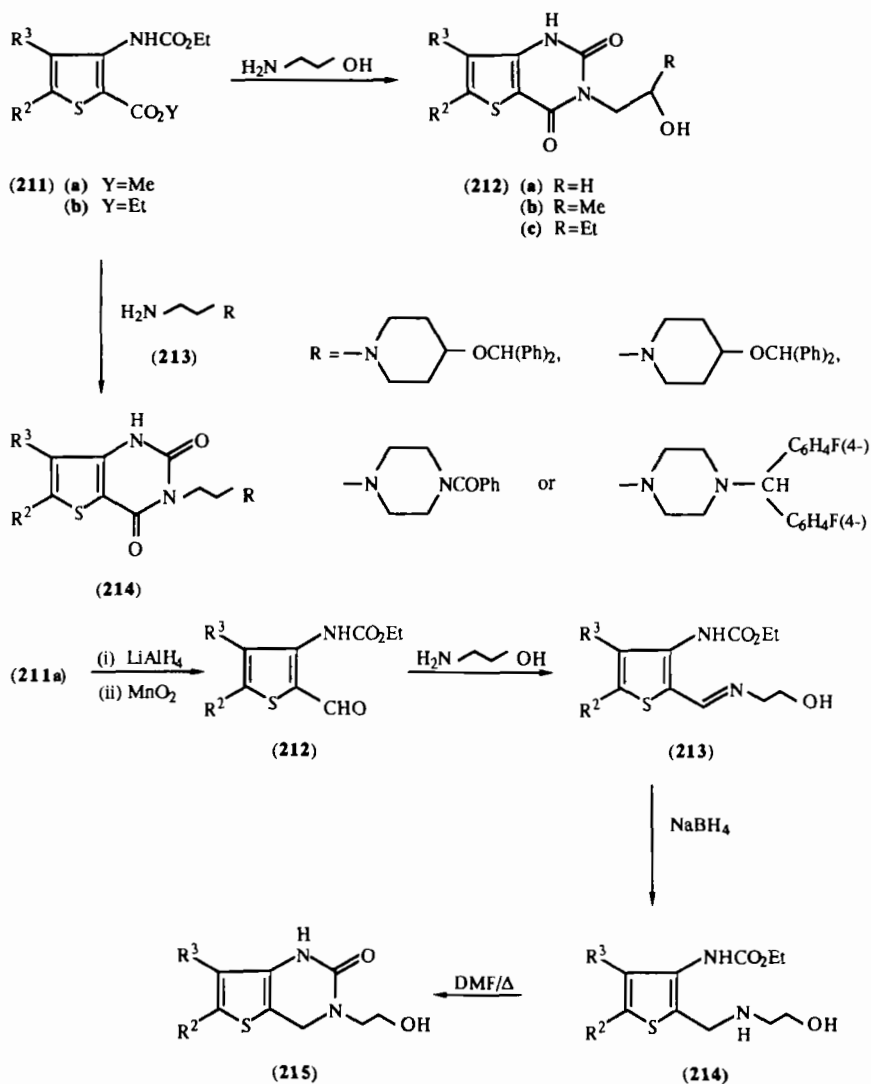
3-Arylpiperazinyethylthieno[3,2-*d*]pyrimidinediones **209** were obtained from *o*-aminoester **189** ( $R^2 = R^3 = \text{H}$ ,  $Y = \text{Me}$ ) in three steps. The latter was reacted with 2-chloroethyl isocyanate to give the 2-chloroethylurea **207**. This urea was then treated with various phenyl-substituted piperazines to afford ureas **208**. These ureas were cyclized to the thienopyrimidinediones **209** by heating in methanolic potassium hydroxide (88JMC1786).

Methyl 3-ethoxycarbonylaminothiophene-2-carboxylates **211a** derived from *o*-aminoesters **189** ( $Y = \text{Me}$ ) and ethyl chloroformate were heated at 130–135°C with ethanolamine to give 3-(2-hydroxyethyl)thienopyrimidine-2(1*H*),4(3*H*)-diones **212** (89CPB1197, 89CPB2091). Several 3-[3-ethyl(4-substituted piperidine or piperazine)thienopyrimidine-2(1*H*),4-diones **214**



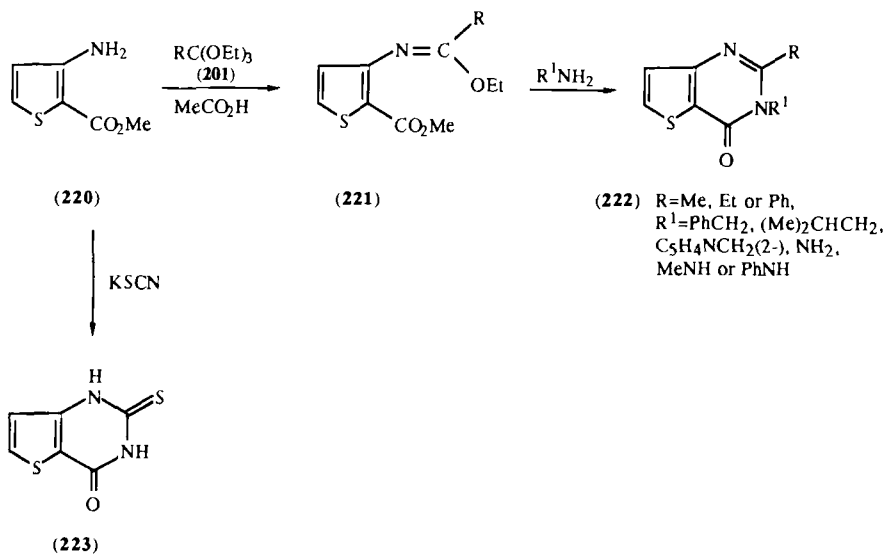
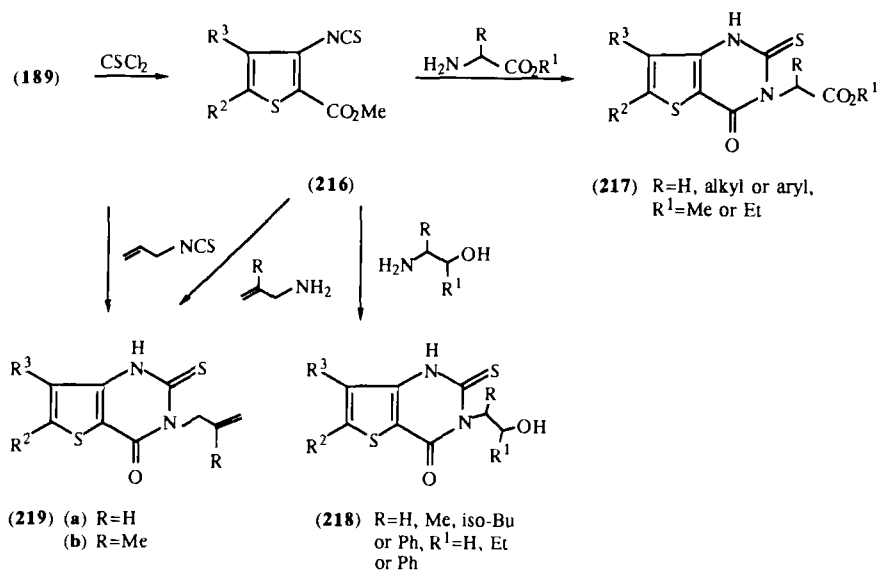
Conditions: (i) NaH/DMF/alkyl halide, (ii) Ac<sub>2</sub>O or NaH/DMF acid chloride

were prepared by heating carbamates **211b** with appropriate amines **213** [89JAP(K)213284]. 3,4-Dihydro-3-(2-hydroxyethyl)thienopyrimidin-2(1*H*)-ones **215** were synthesized by a five-step reaction sequence. Selective reduction of the methoxycarbonyl group of **211a** with lithium aluminum hydride followed by oxidation of the resulting alcohol with manganese(IV) oxide gave the aldehydes **212** in one pot. Condensation of aldehydes **212** with ethanolamine yielded the Schiff bases **213**. Reduction of the imino group of compounds **213** with sodium borohydride afforded



2-(2-hydroxyethylaminomethyl) derivatives **214**. The latter were then heated in DMF to furnish the thienopyrimidones **215** (89CPB2717).

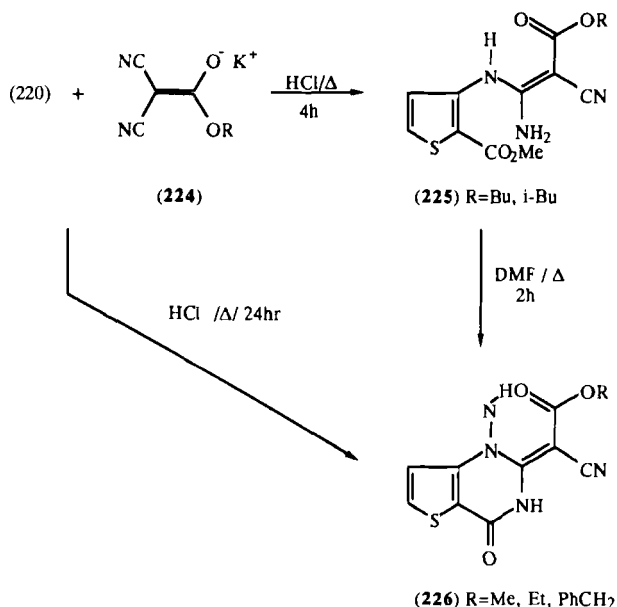
Thienopyrimidin-4-one-2(1*H*)-thiones **217** were prepared by two slightly different methods. Reaction of *o*-aminoesters **189** with thiophosgene gave the isothiocyanates **216** which were heated with a variety of  $\alpha$ -aminoes-



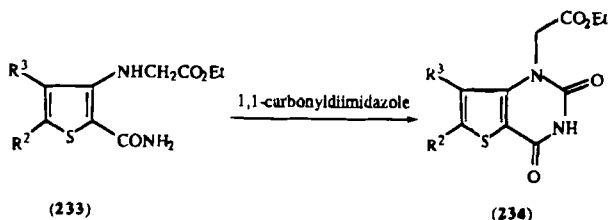
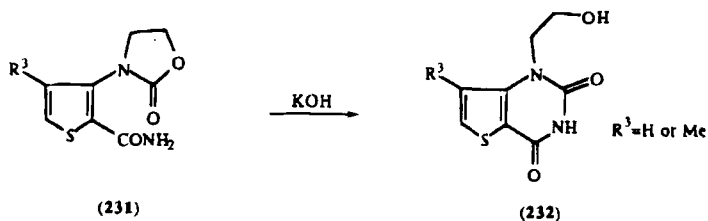
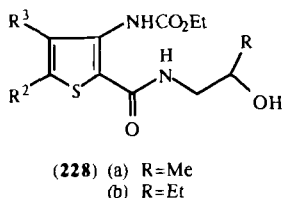
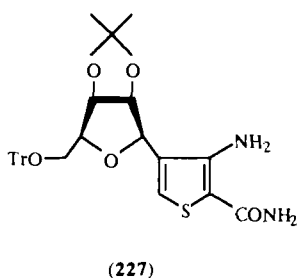
ters or 2-aminoethanols to afford the corresponding 3-substituted thienopyrimidinethiones **217** or **218** (82EUP43054; 89CPB1197, 89CPB2122). By the second method 3-allylthienopyrimidin-4(3*H*)-one-2(1*H*)-thiones **219a** were prepared by treating *o*-aminoesters **189** with allyl isothiocyanate. Thienopyrimidines **219a,b** were also prepared by treating isothiocyanates **216** with the appropriate allyl amines (89CPB2122). Heating methyl 3-aminothiophene-2-carboxylate **220** potassium thiocyanate in methanolic hydrogen chloride afforded thieno[3,2-*d*]pyrimidine-4(3*H*),2(1*H*)-thione **223** directly (90EUP404356).

*o*-Aminoester **220** reacted with a variety of orthoesters in glacial acetic acid to produce *N*-(2-carbomethoxythienyl)imidates **221**. Treatment of these imidates with primary amines, hydrazine, methylhydrazine, or phenyl hydrazine in methanol at room temperature yielded exclusively the thienopyrimidin-4-ones **222**. No isomeric 1,3,4-thienotriazepin-5-ones were detected in these reactions (92BSB445).

Neidlein and Sui (91HCA579) prepared methyl 3-[[2-alkoxycarbonyl]-1-amino-2-cyanoethenyl]amino}thiophene-2-carboxylates **225** by treating the potassium salt of alkyl dicyanoacetates **224** with *o*-aminoester **220** in refluxing hydrochloric acid. Carboxylates **225** were then cyclized to (4-oxothienopyrimidin-2-ylidene)acetates **226** in boiling DMF without catalyst. Prolonged heating of the ester **220** and the salts **224** in hydrochloric acid provided a direct route to the acetates **226**, albeit in lower yield.

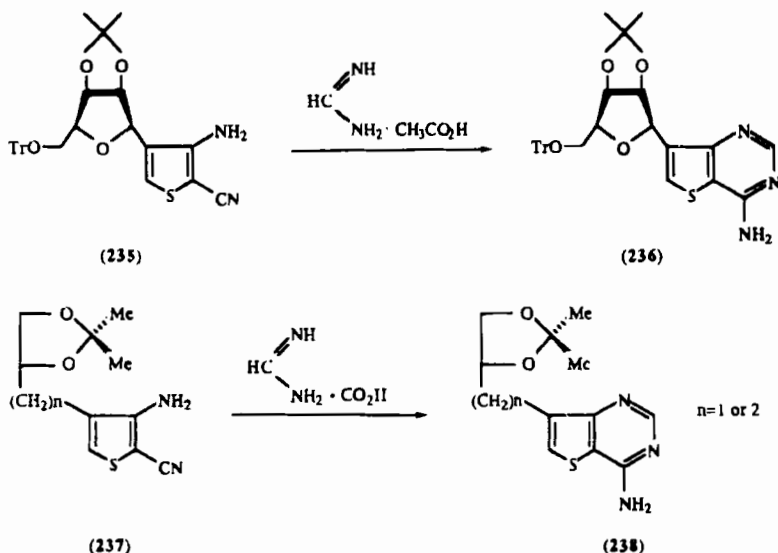


b. *From 3-Aminothiophene-2-carboxamides.* Direct formation of the pyrimidine ring from 3-aminothiophene-2-carboxamides requires reaction with a double electrophilic reagent which provides the remaining one-carbon unit. Indirect formation of the pyrimidine ring involves functionalization of amino and carboxamide groups before ring closure. Therefore, an alternative synthesis of ribofuranosylthienopyrimidin-4(3*H*)-one **195** required heating *o*-aminocarboxamide **227** with triethyl orthoformate at 95°C (82JOC4633; 83EUP71227). Thienopyrimidinediones **188b,c** were



also obtained by cyclizing the respective appropriately substituted *o*-aminocarboxamides **208a,b** in boiling DMF. Cyclization of intermediate **229** by a similar manner gave the 3-(3-chloropropyl)thienopyrimidinedione **230** (89CPB2091). 3-(2-Oxo-3-oxazolidinyl)thiophene-3-carboxamides **231** were cyclized to the corresponding 1-(2-hydroxyethyl)thienopyrimidinediones **232** by boiling in ethanolic potassium hydroxide (89H985). 2-Ethoxycarbonylmethylaminothiophene-3-carboxamide **233** was subjected to ring closure by condensation with 1,1-carbonyldiimidazole to yield the thienopyrimidine **234** (93MI1).

c. *From 3-Aminothiophene-2-carbonitriles.* Formamidine acetate provides the remaining C—N fragment required by 3-aminothiophene-2-carbonitriles **235** and **237** to form the corresponding 4-aminothieno[3,2-*d*]pyrimidines **236** and **238**. The reactions are performed in absolute ethanol at room temperature and under reflux, respectively [83EUP71227; 91JCS(P1)195].



Prolonged heating of *o*-aminonitrile **239a** with trimethyl orthobenzoate at 120°C gave the acetimidate **241a**. Treatment of *o*-aminonitrile **239b** with trimethyl orthoacetate and acetic anhydride at 90°C afforded acetimidate **241b**. Ring closure of imidates **241a,b** with sodium amide and liquid ammonia in a sealed vessel at 80°C, gave the corresponding 4-aminothienopyrimidines **242a,b**. 2-Substituted thienopyrimidine-4(3*H*)-

thiones **245a,b** were obtained by treating 3-acylamino-2-cyanothiophenes **243** with sodium hydrosulfide in ethanol. Acyl compounds **243** were prepared from *o*-aminonitriles **239a,b** by acetylation and benzoylation in pyridine, respectively (86JHC1757). An alternative route to thienopyrimidinethiones **245a,b** involves treating *o*-aminonitriles **239a,b** with a mixture of hydrogen sulfide, pyridine, and triethylamine, and then cyclizing the derived thioamides **244** by heating with trimethyl orthoacetate at 90°C. 2,4-Diaminothienopyrimidines **240** were obtained directly from *o*-aminocarbonitriles **239a,b**, respectively, by treatment of **239a** with guanidine carbonate and sodium ethoxide in refluxing ethanol or by fusion of **239b** with guanidine carbonate (86JHC1757).

4-Substituted aminothieno[3,2-*d*]pyrimidines **247** were obtained from *o*-aminocarbonitriles **246** by a four-step reaction sequence as described for the corresponding thieno[3,2-*d*]pyrimidine isomer **59** (91EUP452002).

## 2. From Pyrimidines

Since the publication of the monograph chapter on thienopyrimidines (84M1), only one paper has appeared on the synthesis of thieno[2,3-*d*]pyrimidines from pyrimidines.

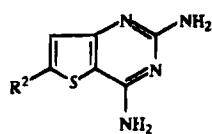
Otter *et al.* (89JHC1851) obtained the thienopyrimidine **253** in 50% yield by heating 5-(2-propynylthio)pyrimidine **248** in DMSO at 145°C. The reaction proceeds via a Claisen rearrangement of **248** in the allene **249**, which then cyclizes to the product **253**. An 18% yield of the thiomethyl compound **252** was also isolated. This was explained by a mechanism involving solvent incorporation into allene **249** to give intermediate **250**; this intermediate then undergoes a Sommelet-Hauser type of rearrangement to afford **251**, which cyclizes to the product **252**.

Heating pyrimidine-5-(2-propynylsulfoxide) **254** in DMSO at 105°C, followed by acidification, gave thieno[3,2-*d*]pyrimidine-7-carbaldehyde **258**. The reaction is postulated to occur via an initial sigmatropic rearrangement to generate the allene **255**, which undergoes a Claisen-like rearrangement to the unsaturated aldehyde **256**. Cyclization of **256** gives the dihydro intermediate **257**, which oxidizes to the product **258**.

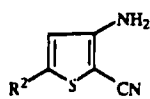
## 3. Miscellaneous Syntheses

6,7-Dihydro-2-methylthiothieno[3,2-*d*]pyrimidin-4(3*H*)-one **259** was synthesized in one step from methyl 2,3,4,5-tetrahydro-3-oxothiophene-2-carboxylate and *S*-methylisothiouronium sulfate in the presence of methanolic potassium hydroxide. The reaction requires stirring at room temperature for 16 h (91MIP1).

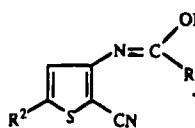




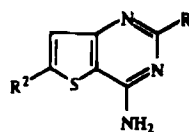
(240)



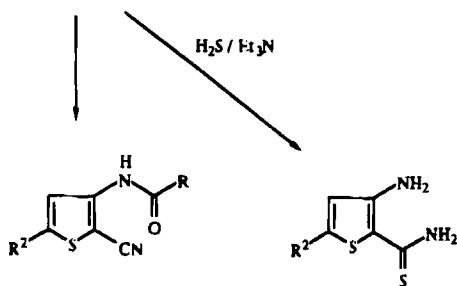
(239) (a)  $\text{R}^2 = \text{Me}$   
(b)  $\text{R}^2 = \text{Ph}$



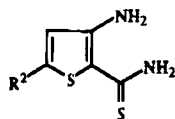
(241) (a)  $\text{R} = \text{Ph}$   
(b)  $\text{R} = \text{Me}$



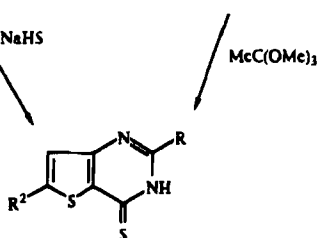
(242) (a)  $\text{R} = \text{Ph}$   
(b)  $\text{R} = \text{Me}$



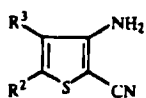
(243)



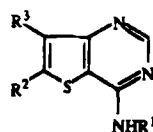
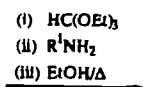
(244)



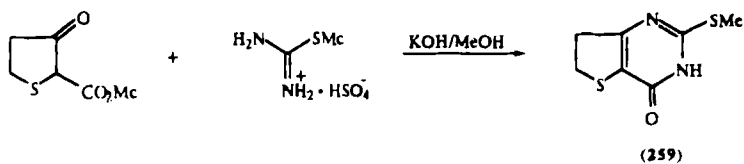
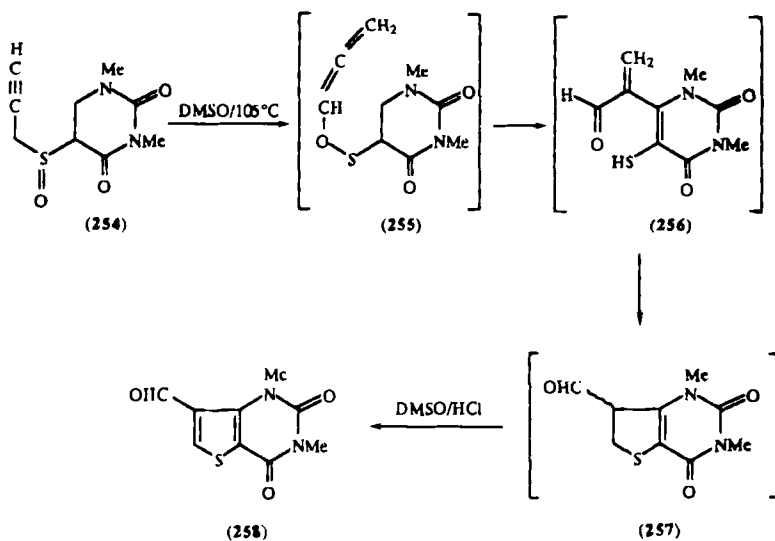
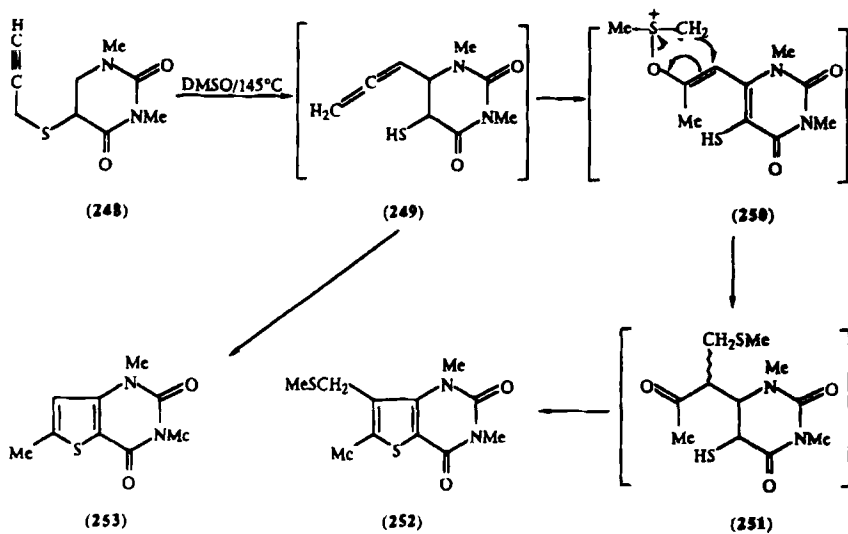
(245) (a)  $\text{R} = \text{Me}$   
(b)  $\text{R} = \text{Ph}$



(246)



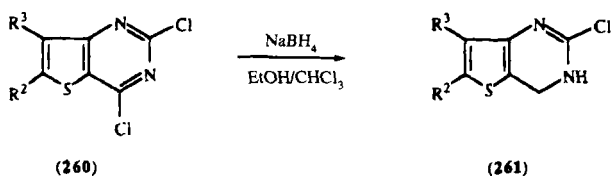
(247)  $\text{R}^1 = \text{alkyl or aryl}$



## B. REACTIONS

## 1. Reduction

2-Chloro-3,4-dihydrothienopyrimidines **261** were obtained by selective reduction of 2,4-dichlorothienopyrimidines **260** in a mixture of ethanol and chloroform at room temperature or 50°C [80EUP8408; 81JAP(K)104870, 81JHC67, 81JMC376].



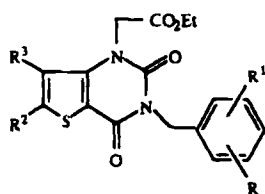
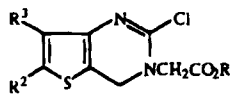
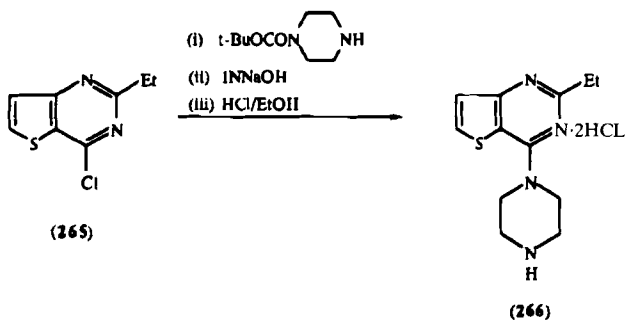
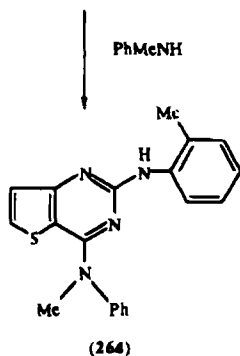
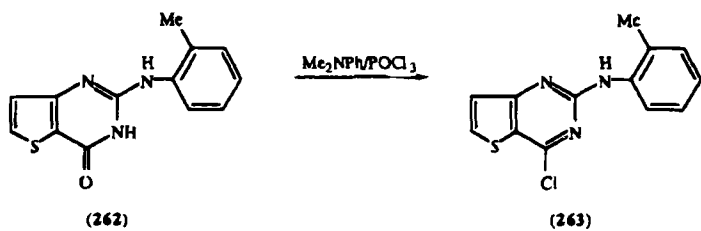
## 2. Ring Chlorination and Nucleophilic Substitution

Heating 2-methylthiothienopyrimidine **259** in *o*-toluidine at 200°C gave the 2-(2-methylphenylamino) derivative **262** (91MIP1). Aromatic analogs of **259** react with a variety of aliphatic and aromatic amines in a similar way (90EUP404356).

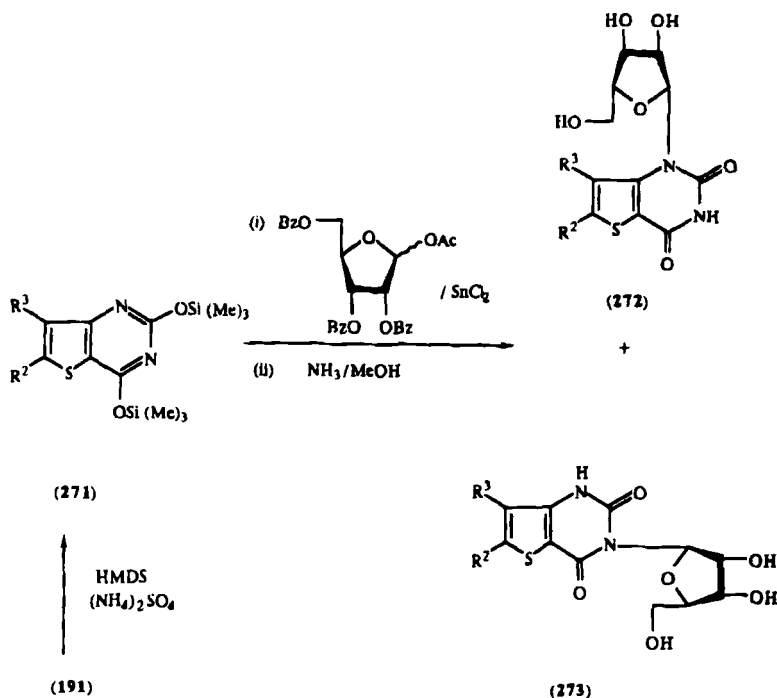
Thienopyrimidin-4(3*H*)-ones **262** and **191b** were chlorinated to the 4-chloro derivatives **263** and **265** by heating in a mixture of *N,N*-di(ethyl or methyl)aniline and phosphoryl chloride. Heating compound **263** with *N*-methylaniline, and compound **265** with 1-*t*-butoxycarbonylpiperazine in isoamyl alcohol followed by treatment with 1 *N* sodium hydroxide and ethanolic hydrogen chloride, afforded the 4-(*N*-methyl-*N*-phenylamino)thienopyrimidine **264** and 4-piperazinothienopyrimidine dihydrochloride **266**, respectively (88EUP276057; 91MIP1). 2,6-Diphenylthienopyrimidine-4(3*H*)-thione **245b** when heated briefly to reflux in a mixture of *N,N*-diethylaniline and phosphoryl chloride gave the 4-chloro derivative **267**. This could be readily ammonolyzed with saturated methanolic ammonia to the 4-amino derivative **268** (86JHC1757).

3. *N*-Alkylation and *S*-Alkylation

Alkylation at position 3 of 2-chloro-3,4-dihydrothienopyrimidines **261** with α-halogeno esters gave the corresponding 3-substituted derivatives **269** [81JAP(K)104870]. Alkylation of thienopyrimidones **234** at position 3 with halogenated benzyl bromides in DMF containing sodium hydride gave 1,3-disubstituted derivatives **270** (93MI1).



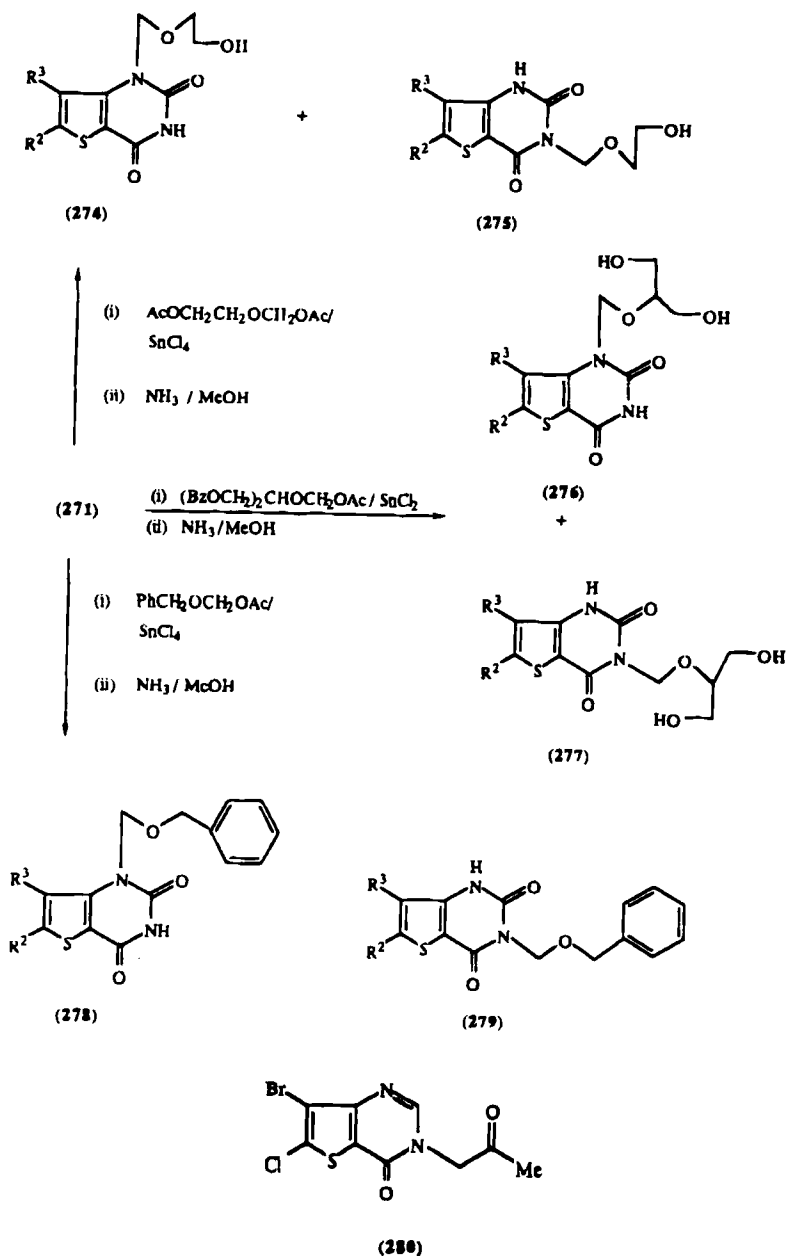
The bis(trimethylsilyl) derivatives **271** resulting from the reaction of thieno[3,2-*d*]pyrimidines **191** with hexamethyldisilazane (HMDS) and a catalytic amount of ammonium sulfate were condensed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranose in the presence of stannic chloride to furnish, after treatment with methanolic ammonia, the 1-( $\beta$ -D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-diones **272** and 3-( $\beta$ -D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-diones **273**.



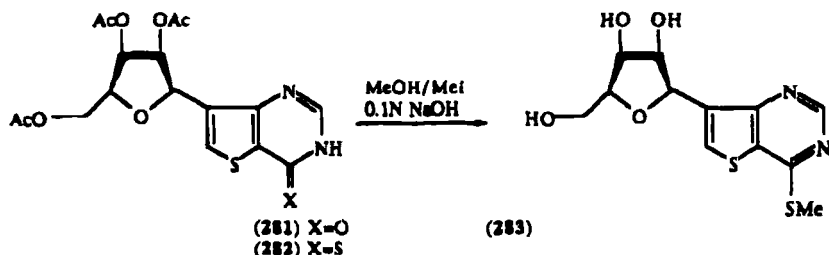
The same experimental procedure was used for further *N*-alkylation reactions of 2,4-bis(trimethylsilyloxy)thieno[3,2-*d*]pyrimidine-2,4-diones **271**. Thus, reaction of **271** with 2-acetoxyethyl acetoxymethyl ether, 2-(acetoxymethoxy)propane-1,3-dibenzoate, and benzyloxymethyl acetate gave the respective 1- and 3-alkylated derivatives **274** and **275**, **276** and **277**, and **278** and **279** (90MI1; 94JHC305; 94MI2, 94MI3).

3-Acetylmethyl-7-bromo-6-chlorothieno[3,2-*d*]pyrimidin-4-one **280** was obtained by alkylation of compound **285** with chloroacetone (88USP 725599).

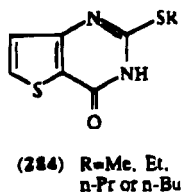
7-(2',3',5'-Tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)thieno[3,2-*d*]pyrimidin-4-(3*H*)-one **281**, (*X* = O) was converted into the corresponding thione derivative **282** (*X* = S) in 84% yield by heating in dioxane containing phosphorus



pentasulfide. The latter was *S*-methylated and deacetylated by treating with methyl iodine in 0.1 *N* sodium hydroxide to give 4-methylthio-7-( $\beta$ -D-ribofuranosyl)thieno[3,2-*d*]pyrimidine **283** (83EUP71227; 86MI3).

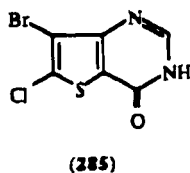


Thieno[3,2-*d*]pyrimidine-2(1*H*)-thiones **217–219** and -4(3*H*)-thiones **245** were *S*-methylated smoothly with methyl iodide in base to the corresponding 2-methylthio (82EUP43054; 89CPB1197) and 4-methylthio (86JHC 1757) compounds. *S*-Alkylation of thieno[3,2-*d*]pyrimidin-4(3*H*)-one-2(1*H*)-thione **223** with alkyl halides in dilute sodium hydroxide solution afforded 2-alkylthio derivatives **284**. Nucleophilic displacement of the alkylthio group in compound **284** by primary amines has also been reported (90EUP404356).



#### 4. Electrophilic Aromatic Substitution

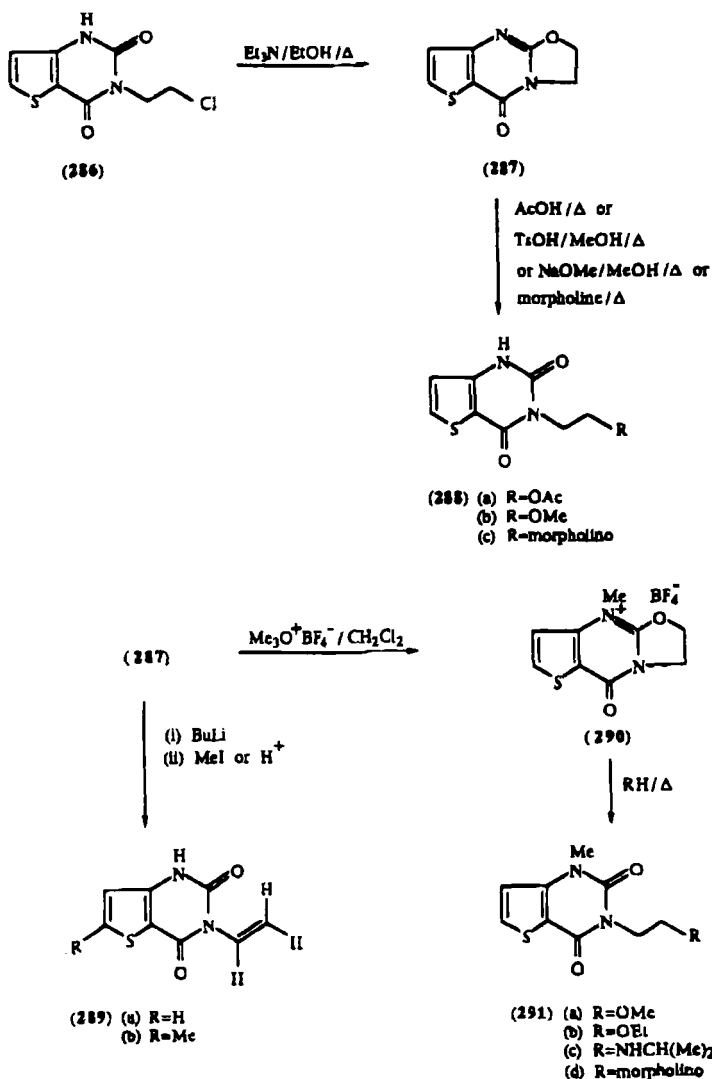
6-Chlorothieno[3,2-*d*]pyrimidin-4(3*H*)-one **190a** ( $R^2 = \text{Cl}$ ,  $R^3 = \text{H}$ ) was converted to the 8-bromo derivative **285** by heating at 80°C in a mixture of bromine and acetic acid (88USP4725599). Thieno[3,2-*d*]pyrimidinedione **270** ( $R = 2 - \text{F}$ ,  $R^1 = 4 - \text{Br}$ ,  $R^2 = R^3 = \text{H}$ ) was chlorinated at position 6 by heating at 60°C with sulfuryl chloride in carbon tetrachloride. The reaction worked equally well with *N*-chlorosuccinimide instead of sulfuryl chloride (93MI1).



#### 5. Miscellaneous Reactions

Several thieno[3,2-*d*]pyrimidines were obtained from addition reactions of various nucleophiles onto position 2 of 2,3-dihydrooxazolo[3,2-

*a*]thieno[3,2-*d*]pyrimidin-5-one **287**. The latter was obtained by treating the 3-(2-hydroxyethyl) derivative **212a** ( $R^2 = R^3 = H$ ) with thionyl chloride to give 3-(2-chloroethyl)thieno[3,2-*d*]pyrimidin-2(1*H*),4-dione **286**, which cyclized by heating in a mixture of triethylamine and ethanol. Thus, reaction of compound **287** with concentrated hydrochloric acid at 100°C gave the chloro compound **286**, whereas reaction with aqueous sodium hydroxide the starting compound **212a** ( $R^2 = R^3 = H$ ). Compound **287** was also





reacted with the following reagents at reflux temperature: acetic acid, *p*-toluenesulfonic acid and sodium methoxide in methanol, or morpholine in ethanol, to give the corresponding derivatives **288a–c**. Lithiation of compound **287** with *n*-butyllithium followed by protonation with glacial acetic acid or methylation with methyl iodide afforded derivatives **289a** and **289b**, respectively. Furthermore, treatment of compound **287** with trimethyloxonium tetrafluoroborate in dichloromethane produced the quaternary salt **290**. Reaction of salt **290** with alcohols or amines proceeded smoothly and gave the 1-methyl-3-substituted thieno[3,2-*d*]pyrimidinediones **291** (89-CPB1197).

### C. PHYSICOCHEMICAL PROPERTIES

**UV data:** 82JOC4633; 86JHC1757, 86MI3; 89CPB1197, 89JHC1851; 90MI1; 91HCA579, 91JCS(P1)195; 92PHA577; 94JHC305, 94MI2, 94MI3.

**IR data:** 86MI3; 88JMC1786; 89CPB1197, 89CPB2091, 89CPB2122, 89CPB2717, 89H985; 90MI1; 91HCA579, 91JCS(P1)195, 91JMC1492; 92BSC445, 92PHA577; 94JHC305, 94MI2, 94MI3.

**<sup>1</sup>H-NMR data:** 82JOC4633; 86JHC1757, 86MI3; 88JMC1786; 89-CPB1197, 89CPB2091, 89CPB2122, 89CPB2717, 89H985, 89JHC1851; 90MI1; 91HCA579, 91JCS(P1)195, 91JMC1492; 92BSC445; 94JHC305, 94MI2, 94MI3.

**<sup>13</sup>C-NMR data:** 86MI3; 89JHC1851; 90MI1; 91HCA579; 94JHC305, 94MI2, 94MI3.

**Mass spectral data:** 86MI3; 89CPB1197; 90MI1; 91HCA579, 91-JCS(P1)195, 91JMC1492; 92PHA577; 94MI2.

### D. APPLICATIONS

The following biological effects of thieno[3,2-*d*]pyrimidines are mentioned in patents:  $\beta$ -adrenergic blocker (88EUP276057); angiotensin II receptor blocker (93MIP1); antitumor (83EUP71227); choline acetyltransferase stimulatory (91USP5075305); coccidiostatic (88USP4725599); and fungicidal, insecticidal, and muticidal (91EUP452002). 2-4-Dimethylthio-6-phenylthieno[3,2-*d*]pyrimidine was patented as nonlinear optic material (92JAP4305630).

7-( $\beta$ -D-Ribofuranosyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one **266**, which proved active against pathogenic hemoflagellates, shows promise as a potential antiprotozoan drug owing to its low toxicity to mammalian cells (84AAC292; 85JBC9660; 86MI3). The same compound was found to be a weak inhibitor of purine nucleoside phosphorylase (86MI2), but was incorporated as a purine analog into the nucleotide pool of *Schistosoma*

*mansoni* when coadministered with a nucleoside transport inhibitor. The results show a highly selective toxicity against the schistosome and not the mammalian cells (87BP1089).

Several thieno[3,2-*d*]pyrimidine-2,4-diones **267** were evaluated *in vitro* for their ability to inhibit enzymatic activity on partially purified bovine lens aldose reductase. A high level of *in vitro* activity was demonstrated ( $IC_{50} \approx 10^{-6}$  to  $4 \times 10^{-8}$  M) (91JMC1492; 93MI1).

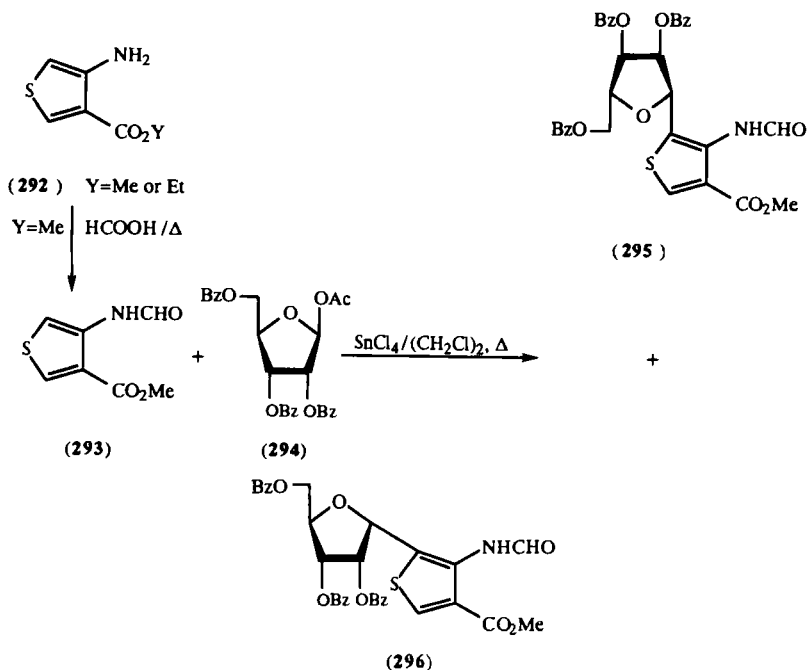
Thieno[3,2-*d*]pyrimidinediones **209**, **210** were found to be potent antihypertensive agents (88JMC1786) whereas thieno[3,2-*d*]pyrimidinediones **202** were potent as selective 5-HT<sub>2</sub> antagonists (91MI1).

## IV. Thieno[3,4-*d*]pyrimidines

### A. SYNTHESIS

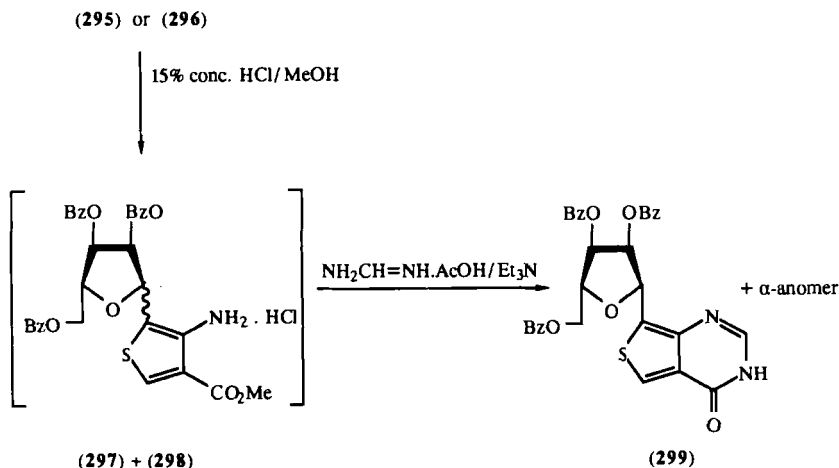
#### 1. From Thiophenes

a. *From Alkyl 3-Aminothiophene-4-carboxylates.* A general approach to the synthesis of thieno[3,4-*d*]pyrimidines comprises the reaction of alkyl 3-aminothiophene-4-carboxylates **292** with electrophilic and/or nucleophilic



reagents that furnish the remaining C and N atoms of the pyrimidine ring. Glycosylation of thiophene **293** with ribose **294** in the presence of stannic chloride as catalyst gave a mixture of 5-(2,3,5-tri-*O*-benzoyl- $\beta$ (and  $\alpha$ )-D-ribofuranosyl)-4-(formylamino)thiophene-3-carboxylates **295** and **296**.

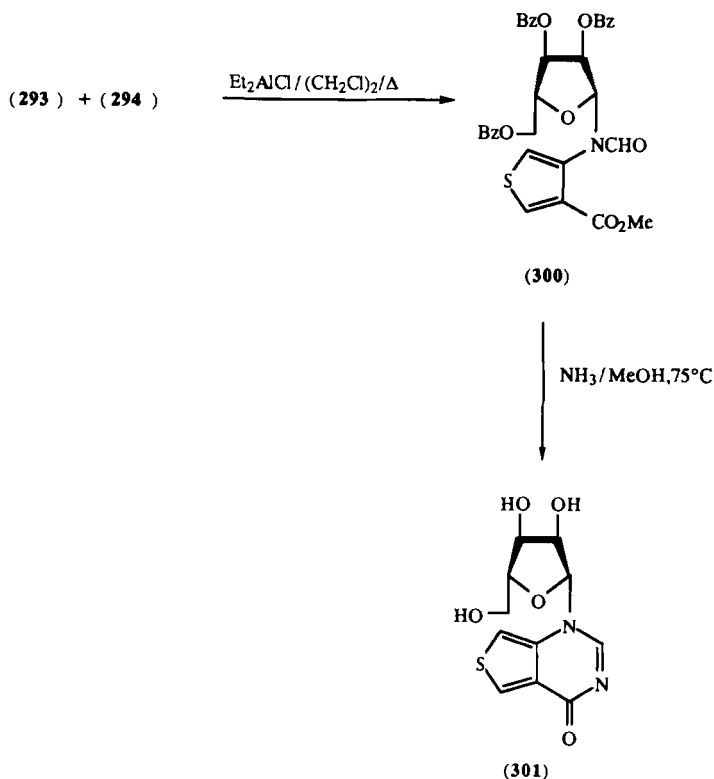
These anomers were separated by chromatography, whereupon each one deformylated with methanolic hydrogen chloride to give an inseparable anomeric mixture of hydrochlorides **297** and **298**. The latter was reacted with formamidine acetate and triethylamine in refluxing ethanol to give directly 7-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)thieno[3,4-*d*]pyrimidin-4(3*H*)-one **299** and its  $\alpha$ -anomer.



Debenzoylation of the ribose moiety in each of these compounds was also reported. The use of diethylaluminum chloride as a catalyst in the glycosylation of **293** by **294** led to the exclusive formation of *N*-glycosylated thiophene **300**. Heating **300** with methanolic ammonia at 75°C afforded 1- $\beta$ -D-ribofuranosylthieno[3,4-*d*]pyrimidin-4(1*H*)-one **301** as the main product (88TL3537; 90MI7).

*Note:* In a recent paper the solvent used for the condensation of **293** and **294** with stannic chloride as catalyst was changed from 1,2-dichloromethane to nitromethane. This improved the yield of the anomeric mixture **295** and **296** by at least 22% (93JHC509).

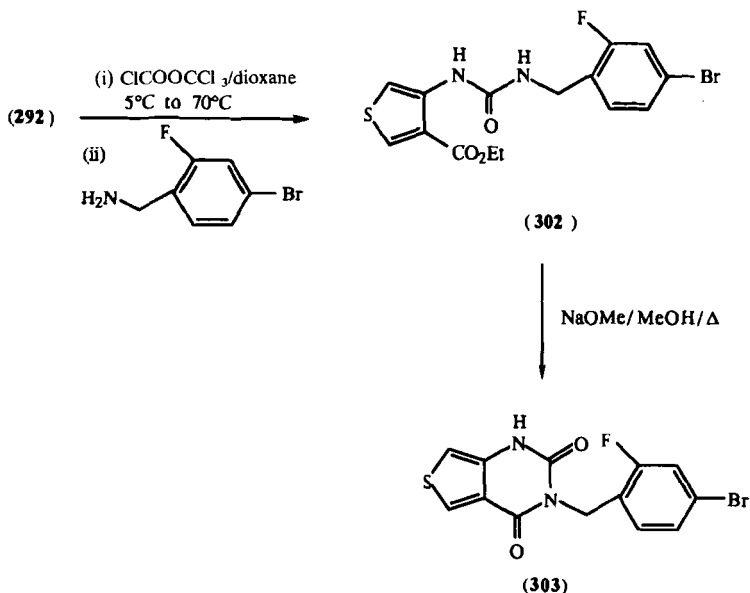
Ogawa *et al.* (93MI1) obtained 3-(4-bromo-2-fluorobenzyl)thieno[3,4-*d*]pyrimidine-2(1*H*),4-dione **303** from *o*-aminoester **292** (*R* = Et) in two steps. The latter was reacted gradually from 5°C to 70°C with trichloro-



methyl chloroformate and then with 4-bromo-2-fluorobenzylamine to afford the urea **302**. Heating this compound with methanolic sodium methoxide gave the product **303** in 75% yield.

Press *et al.* (87USP4670560; 88JMC1786) reacted aminoesters **292** with 2-chloroethyl isocyanate in refluxing toluene and obtained the 2-chloroethylureas **304**. These ureas were further reacted with various *N*-phenyl-substituted piperazines in either THF or propan-2-ol and in the presence of sodium iodide and sodium bicarbonate. The resulting substituted ureas **305** were then heated in methanolic potassium hydroxide to afford the thieno[3,4-*d*]pyrimidinediones **306**.

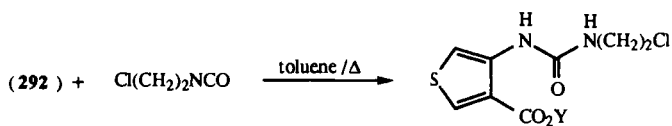
Brown *et al.* have patented (90EUP404356) a short route to potassium thieno[3,4-*d*]pyrimidin-4(1*H*)-one-2-thiolate **308** which involves heating aminoester **292** ( $\text{Y} = \text{Me}$ ) with benzoyl isothiocyanate in refluxing toluene and then cyclizing the resulting thiourea **307** by heating with methanolic potassium hydroxide.



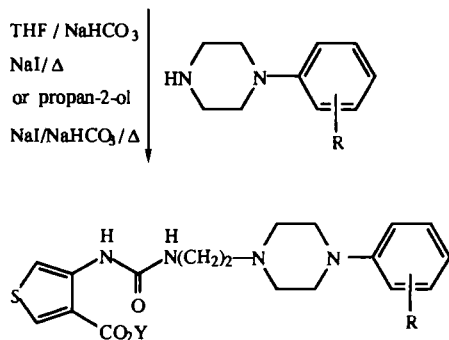
Two synthetic routes for 3-[4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl]-thieno[3,4-*d*]pyrimidine-2,4-dione **316** were described by Russell *et al.* (90JHC1761). Carbamate **310a**, prepared by treating a mixture of amine hydrochloride **309** and ethyl chloroformate with dilute sodium hydroxide, was reacted with 4-[(2-methoxyphenyl)piperazin-1-yl]butanamine **313** in the presence of trimethylaluminum/toluene. The yield of **316** was a modest 20%. However, when bromobutyl urea **314** was heated with 1-(2-methoxyphenyl)piperazine hydrochloride **315** in the presence of sodium bicarbonate and sodium iodide in propan-2-ol, compound **316** was obtained in 84% yield. The first route was also used to synthesize thieno[3,4-*d*]pyrimidine-2,4-dione **312** in 36% yield from **310a** and 4-(2-methoxyphenyl)-1-piperazinethanamine **311**.

Several compounds with various substituents on the piperazine ring of **311**, or instead with a substituted piperidine ring, have been patented [89JAP(K)213284]. Thieno[3,4-*d*]pyrimidin-2,4-dione **318** was synthesized in 91% yield from bromopentyl urea **317** and 1-(2-methoxyphenyl)piperazine hydrochloride **315** using the second method. In a more recent publication (92SC3221) the same authors report the cyclization of the amide **319** into the thieno[3,4-*d*]pyrimidine-2(1*H*),4-dione **320** using methanolic sodium hydroxide.

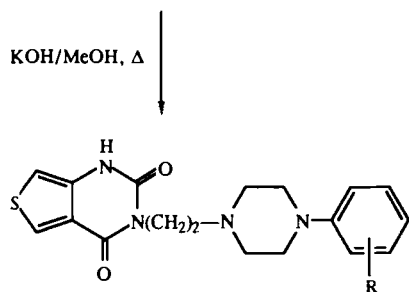
Heating carbamate **310a** with ethanolamine gave 3-(2-hydroxyethyl)thieno[3,4-*d*]pyrimidine-2(1*H*),4(3*H*)-dione **333a**. The 3-(2-hydroxypro-



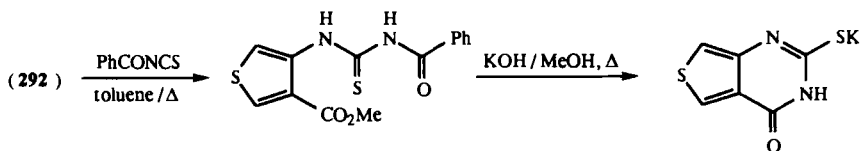
(304) Y=Me or Et



(305) Y=Me or Et

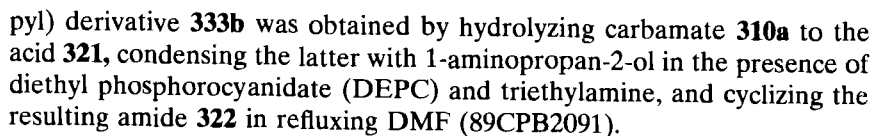


(306) R=H, 4-F, 2-Cl,  
3-Cl, 4-Cl, 2-Me,  
2-OMe, 3-OMe, 4-OMe, 2-OEt



(307)

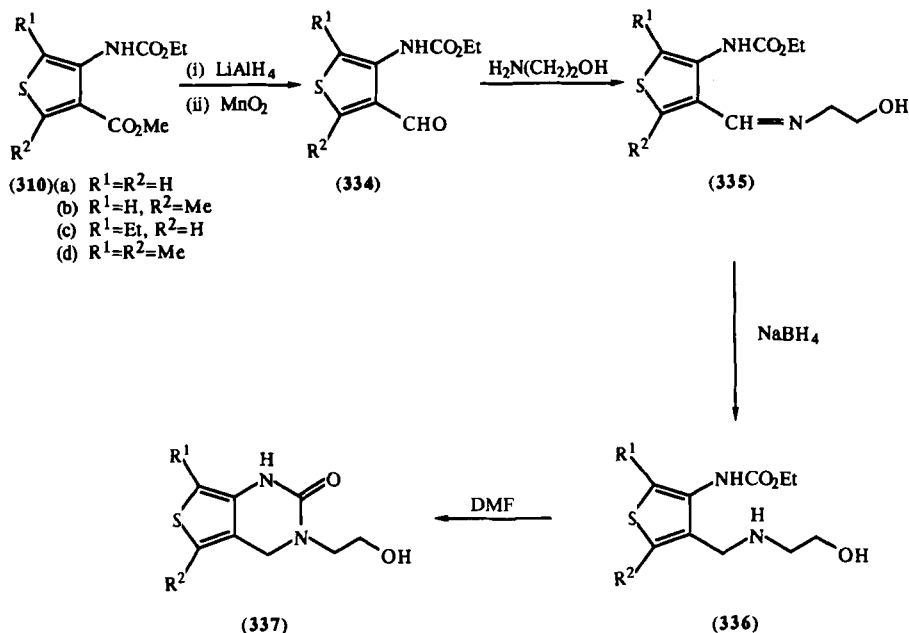
(308)





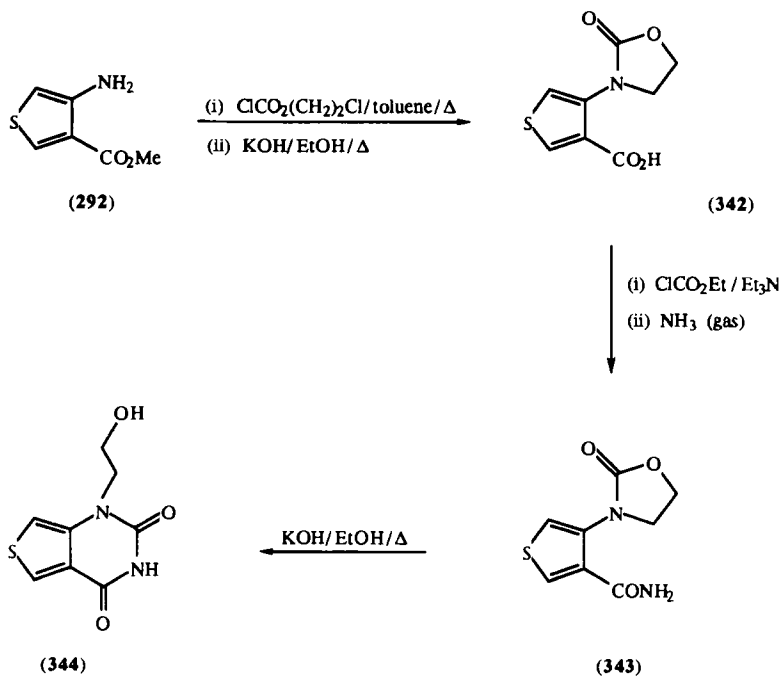
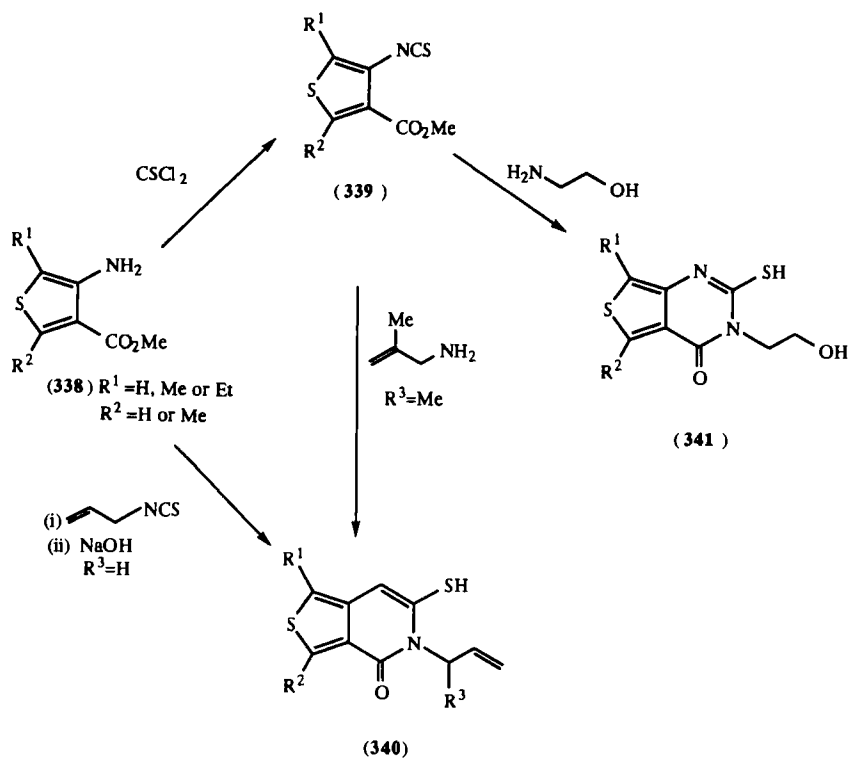


give the (2-hydroxyethyl)aminomethyl derivatives **336**. Cyclization of these compounds into thieno[3,4-*d*]pyrimidin-2-ones **337** required heating in DMF (89CPB2717).



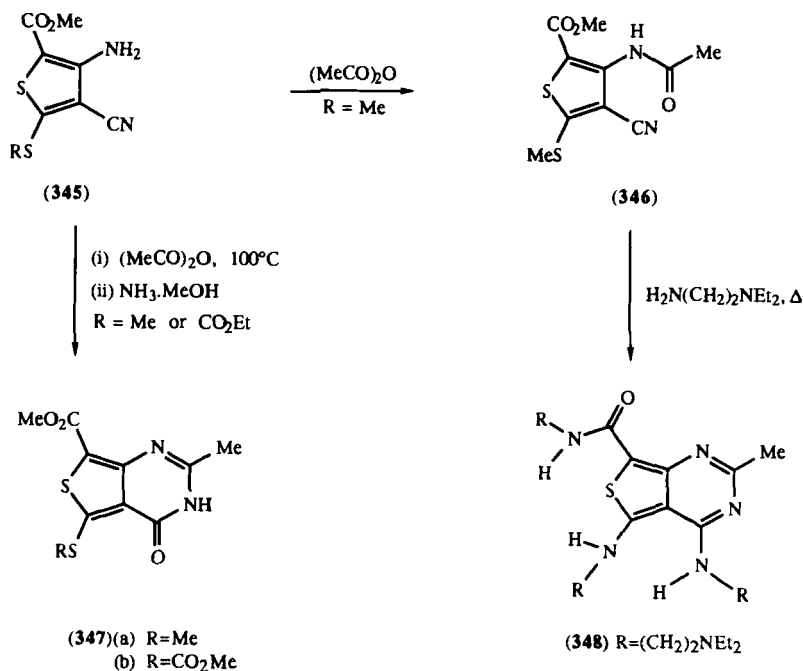
Treatment of *o*-aminoesters **338** with thiophosgene in chloroform afforded isothiocyanates **339**, which were either refluxed with 2-methylallylamine in dichloromethane to afford 3-(2-methyl-2-propenyl)thieno[3,4-*d*]pyrimidin-4-ones **340**, or treated with ethanolamine to yield the 3-(2-hydroxyethyl) derivatives **341**. Derivatives **340** were obtained directly from *o*-aminoesters **338** by heating with allylisothiocyanate in propan-1-ol (89CPB2122).

b. *From 3-Aminothiophene-4-carboxamides.* The one-carbon unit required by 3-aminothiophene-4-carboxamides to form the pyrimidine ring of thieno[3,4-*d*]pyrimidines is supplied by a double electrophilic reagent. This type of reaction has been reported only by Fukumi *et al.* (89H985). On heating in toluene, *o*-aminoester **292** and 3-chloroethyl chloroformate gave the intermediate 2-chloroethylcarbamate derivative, which was hydrolyzed and cyclized with ethanolic potassium hydroxide to afford 3-(2-oxo-3-oxazolidinyl)thiophene-4-carboxylic acid **342**. Amide **343** was prepared from the acid **342** by the formation of mixed anhydride with ethyl chloro-



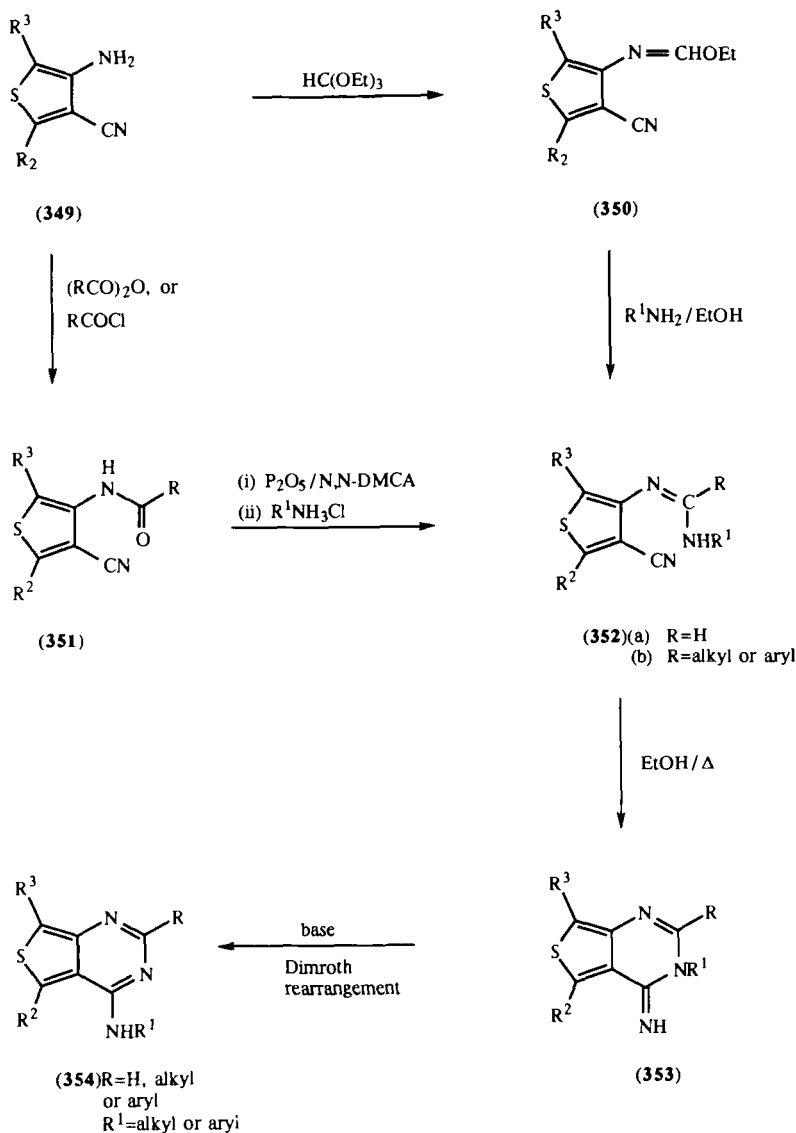
formate followed by treatment with ammonia. Heating amide **343** with ethanolic potassium hydroxide afforded 1-(2-hydroxyethyl)thieno[3,4-*d*]-pyrimidin-2,4(3*H*)-dione **344**.

c. *From 3-Aminothiophene-4-carbonitriles*. Two papers describe the synthesis of thieno[3,4-*d*]pyrimidines from 3-aminothiophene-4-carbonitriles. Briel *et al.* (92PHA577) synthesized three derivatives of the thieno[3,4-*d*]pyrimidine ring system, compounds **347a,b** and **348**, by essentially the same method. The *o*-aminocarbonitriles **345** were heated with acetic anhydride at 100°C. Then, without characterizing the intermediate amides, these authors introduced methanolic ammonia into the reaction mixture to obtain thieno[3,4-*d*]pyrimidin-4(1*H*)-ones **347a,b**. To synthesize thieno[3,4-*d*]pyrimidine **348**, *o*-aminocarbonitrile **345** (R = Me) was heated with acetic anhydride and the resulting amide **346** was cyclized by refluxing with *N,N*-diethylaminoethylamine.



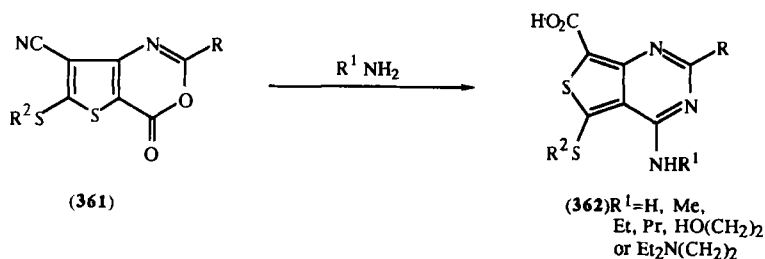
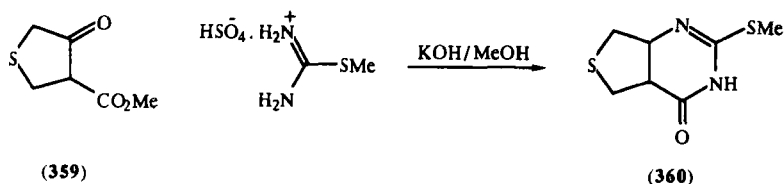
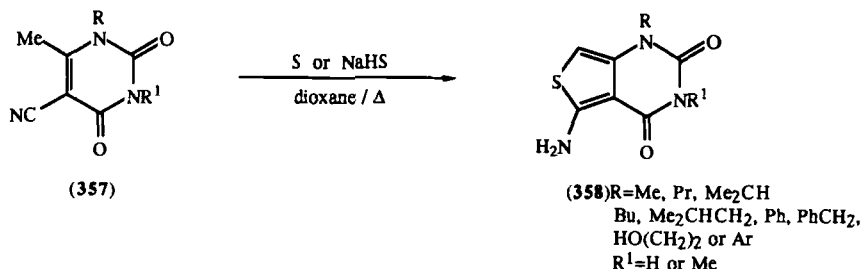
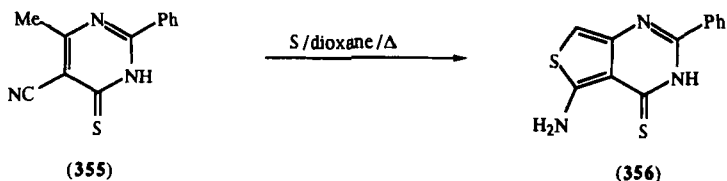
Two approaches leading to 4-iminothieno[3,4-*d*]pyrimidines **353** via *o*-cyanoamidines **352** were patented by Edie *et al.* (91EUP452002). Amidines **352** were prepared either from *o*-cyanocarbonitriles **349** and triethyl orthoformate followed by treatment of the resulting iminoethers **350** with primary

amines, or by treatment of the acylamino derivatives **351** first with a mixture of phosphorus pentoxide and *N,N*-dimethylcyclohexylamine (*N,N*-DMCA) and then with primary amine hydrochlorides (91EUP452002). *o*-Cyanoamidines **352** were cyclized to the 4-iminothieno[3,4-*d*]pyrimidines **353** by refluxing in ethanol. Compounds **353** rearrange to 4-substituted aminothieno[3,4-*d*]pyrimidines **354** by treatment with base.



## 2. From Pyrimidines

The three examples of thieno[3,4-*d*]pyrimidine synthesis from pyrimidines involve fusion of sulfur onto an *o*-cyanomethyl moiety. Elnagdi and Erian (90LA1215) prepared the thieno[3,4-*d*]pyrimidine-7(1*H*)-thione **356** directly from 5-cyano-6-methylpyrimidine **355** and elemental sulfur, in a yield of 52%, by heating in dioxane in the presence of triethylamine. Yu *et al.* (90MI1; 91MI3) cyclized 5-cyano-6-methylpyrimidine-2,4-diones **357** with either elemental sulfur or sodium hydrogen sulfide, obtaining good yields of the thieno[3,4-*d*]pyrimidine-2,4-diones **358**.



### 3. Miscellaneous Syntheses

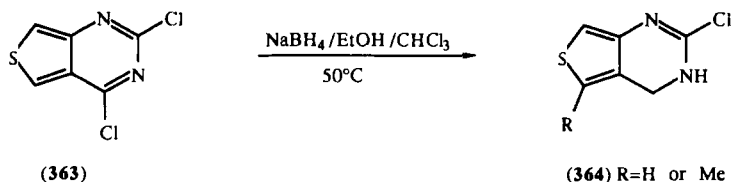
Ketoester **359** reacted with *S*-methylisothiouronium sulfate in methanolic potassium hydroxide at room temperature to give 5,7-dihydro-2-methylthiothieno[3,4-*d*]pyrimidin-4(3*H*)-one **360** (91MIP1).

Briel *et al.* (90GEP282011) describe the transformation of thieno[3,2-*d*]-1,3-oxazin-4-ones **361** into thieno[3,4-*d*]pyrimidines **362** by heating with ammonia saturated DMF or with primary amines. This transformation is an example of an ANRORC reaction.

## B. REACTIONS

### 1. Reduction

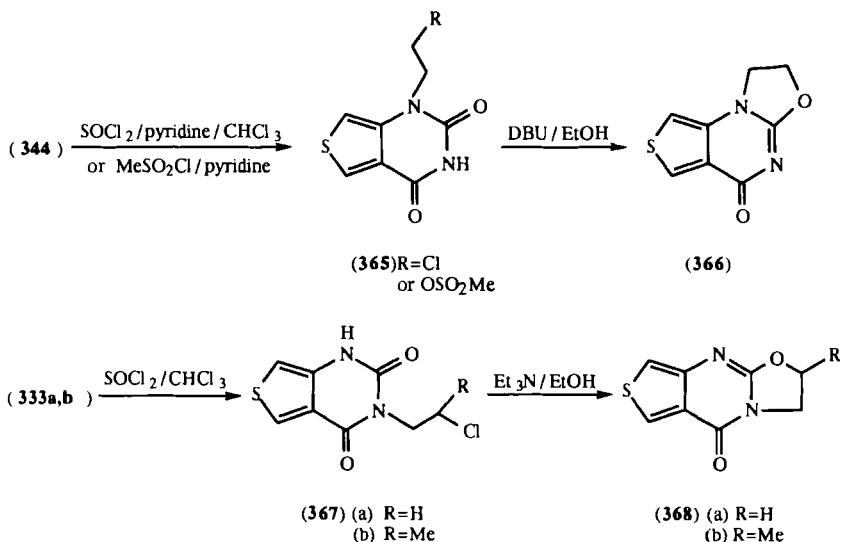
Reduction of 2,4-dichlorothieno[3,4-*d*]pyrimidines **363** with sodium borohydride in a solution of chloroform and ethanol at around 50°C gave the 2-chloro-3,4-dihydro derivatives **364** [80EUP8408; 81JAP(K)-104870, 81JHC67, 81JMC376]. This result reflects the greater reactivity of the 4-chloro atom—a reactivity that also obtains for the other two 2,4-dichlorothienopyrimidine isomers and for the 2,4-dichloropyrimidine derivatives.



### 2. Chlorination and Nucleophilic Substitution

The hydroxy group of 1-(2-hydroxyethyl)thieno[3,4-*d*]pyrimidine-2,4(3*H*)-dione **344** was chlorinated with thionyl chloride in a mixture of pyridine and chloroform, or mesylated with methanesulfonyl chloride in pyridine. No ring chlorination was observed under these conditions. The resulting 1-(2-chloro or 2-methanesulfonyl)ethyl derivative **365** was cyclized to 1,2-dihydrooxazolo[2,3-*b*]thieno[3,4-*d*]pyrimidin-5-one **366** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (89H985). A similar transformation of 3-(2-hydroxyethyl)thieno[3,4-*d*]pyrimidine-2(1*H*),4-diones **333a,b** into the 3-(2-chloroethyl) derivatives **367** with thionyl chloride occurred in chlo-

roform. Cyclization of compounds **367** into 2,3-dihydrooxazolo[3,2-*a*]thieno[3,4-*d*]pyrimidin-5-ones **368a,b** required heating in a mixture of triethylamine and ethanol (89CPB2091).

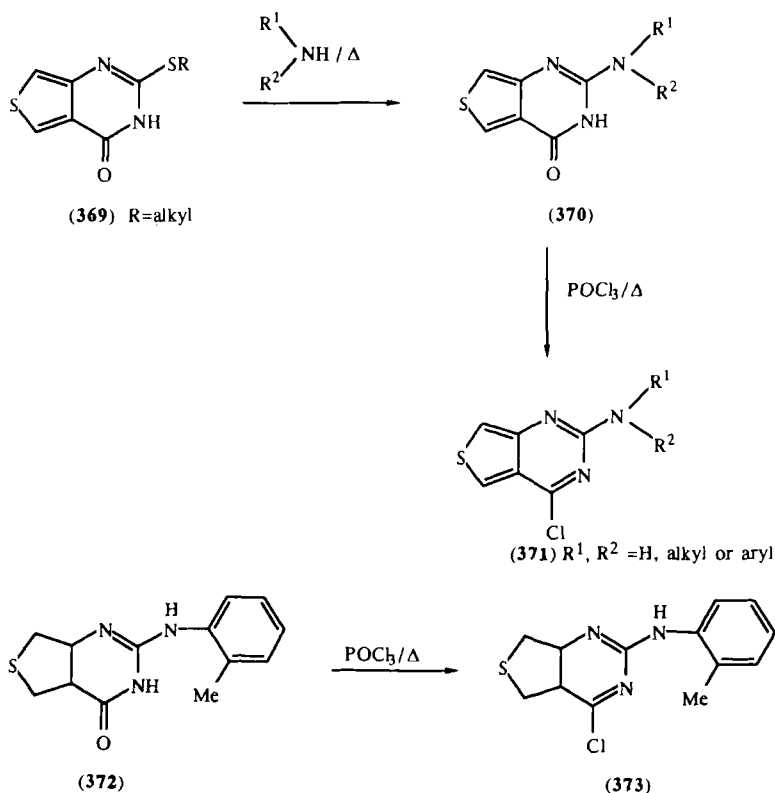


Ring chlorination of 2-amino(or substituted amino)thieno[3,4-*d*]pyrimidin-4(3*H*)-ones **370** (90EUP404356) and 5,7-dihydro-2-(2-methylanilino)thieno[3,4-*d*]pyrimidin-4(3*H*)-one **372** (91MIP1) in boiling phosphoryl chloride gave the respective 4-chloro compounds **371** (90EUP404356) and **373** (91MIP1). The displacement of chlorine from both these compounds by a variety of nucleophiles was also reported.

### 3. *N*-Alkylation, *N*-Acylation, *S*-Alkylation, and Nucleophilic Substitution

3,4-Dihydrothieno[3,4-*d*]pyrimidines **364** were *N*-alkylated at position 3 with a variety of  $\alpha$ -halogeno esters in the presence of base [81JAP(K)104870].

3-Substituted thieno[3,4-*d*]pyrimidine-2(1*H*),4-diones **306** and **312** were alkylated at position 1 with alkyl halides, in DMF, DMSO or THF, in the presence of sodium hydride (87USP4670560; 88JMC1786; 90JHC1761; 91MI1). The alkylation of compound **303** with ethyl bromoacetate in DMF in the presence of sodium hydride produced derivative **381** (93MI1). Alkylation of *N*-3-protected thieno[3,4-*d*]pyrimidine **320** with 1-bromo-2-chloroethane in dimethyl sulfoxide containing sodium hydride, afforded 1-(2-chloroethyl)-3-(2,4-dimethoxyphenylmethyl)thieno[3,4-*d*]pyrimidine-



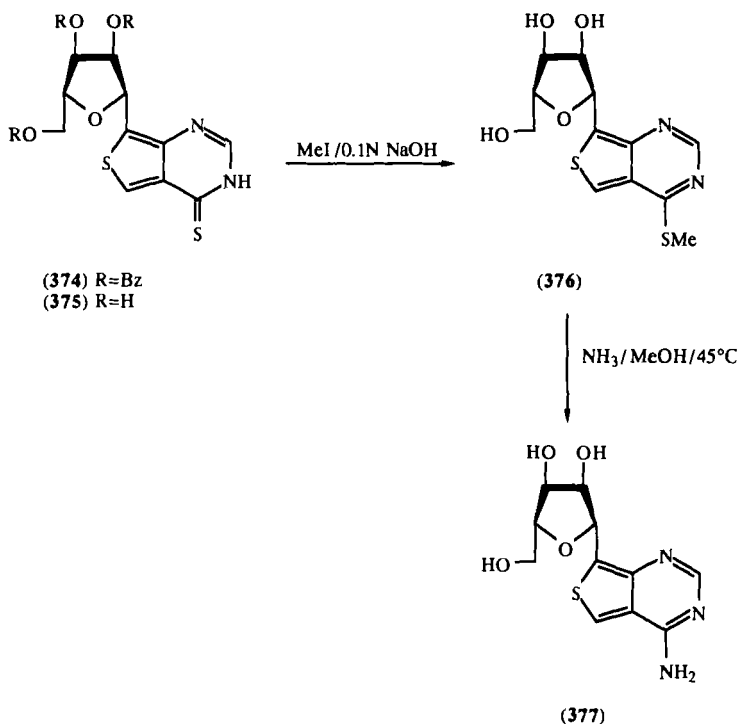
2,4-dione **383** (92SC3221). Compound **318** was also acylated at N-1 with either acid anhydrides, or acid chlorides in dichloromethane/triethylamine or DMF/sodium hydride mixtures (88JMC1786).

The reaction of the salt **308** with alkyl halides in base gave the corresponding 2-alkylthiothieno[3,4-*d*]pyrimidin-4(3*H*)-ones **369**. Heating the latter with ammonia or amines afforded 2-amino(or substituted amino)thieno[3,4-*d*]pyrimidin-4(3*H*)-ones **370** (90EUP404356). When 2-methylthiothieno[3,4-*d*]pyrimidin-4(3*H*)-one **360** was heated with *o*-toluidine at 200°C, displacement of the 2-methylthio group afforded compound **372** (91MIP1).

Heating compound **299** with phosphorus pentasulfide in a mixture of dioxane and pyridine gave 7-(2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranosyl)thieno[3,4-*d*]pyrimidin-4(3*H*)-thione **374**, in 49% yield. Thione **375**, obtained by debenzoylating compound **374**, was converted into the 4-methylthio-7-β-*D*-ribofuranosylthieno[3,4-*d*]pyrimidine **376** by reaction with excess methyl iodide in 0.1 *N* aqueous sodium hydroxide. Substitution of the



4-methylthio group in compound **376** by an amino group required heating in methanolic ammonia at 45°C. 4-Amino-7-β-D-ribofuranosylthieno[3,4-*d*]pyrimidine **377** was isolated in 81% yield. Similar reactions for the α-anomer of compound **299** have also been reported (93JHC509).

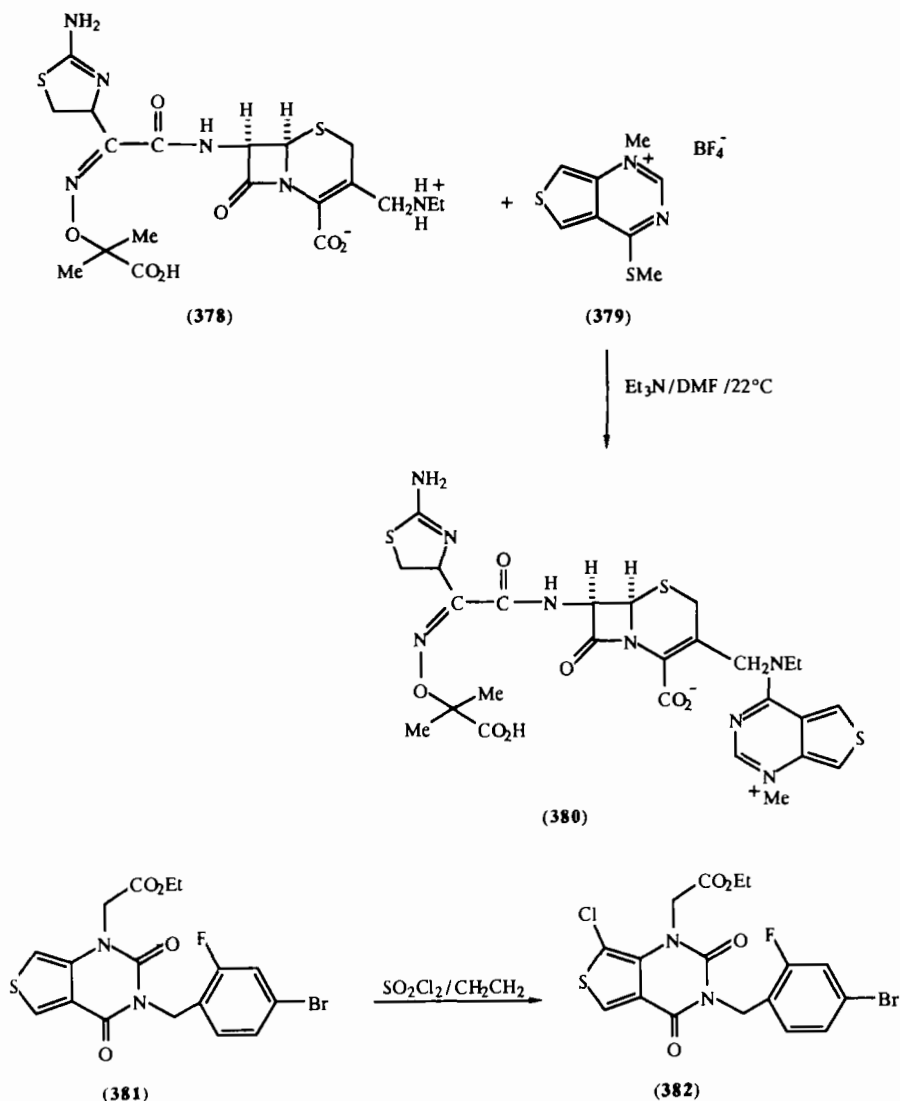


Reaction of 1-methyl-4-methylthiothieno[3,4-*d*]pyrimidine tetrafluoroborate **379** with 3-ethylaminomethylceph-3-em-4-carboxylic acid **378** in DMF at room temperature in the presence of triethylamine, afforded the cephalosporin derivative **380** (87EUP225182).

#### 4. Miscellaneous Reactions

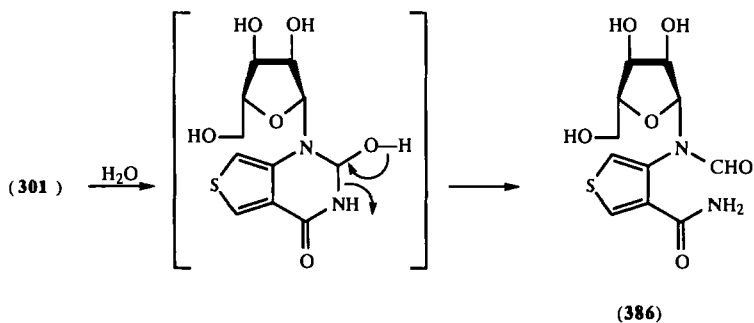
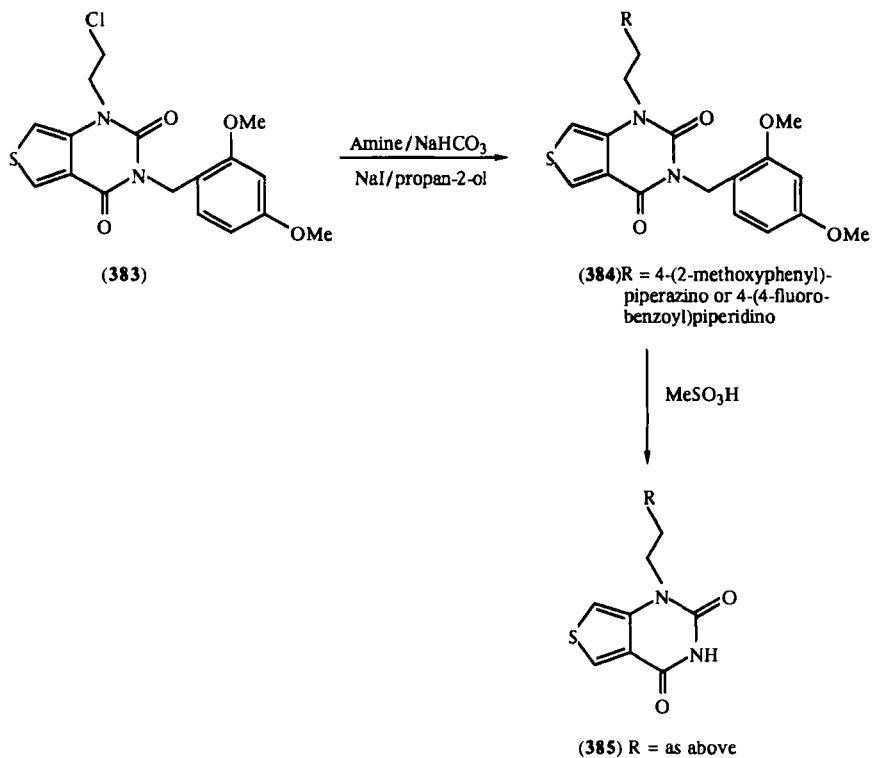
Chlorination at position 4 of thieno[3,4-*d*]pyrimidine **381** with sulfuryl chloride in dichloromethane gave product **382** in 51% yield (93MI1).

The chloro moiety of thieno[3,4-*d*]pyrimidine **383** was displaced by 4-(2-methoxyphenyl)piperazine or 4-(4-fluorobenzoyl)piperidine in refluxing propan-2-ol containing sodium bicarbonate and a catalytic amount of sodium iodide. The N-3 protecting group of the resulting derivatives **384** was



readily removed in methanesulfonic acid to give the thieno[3,4-*d*]pyrimidine-2,4(3*H*)-diones **385** (92SC3221).

Addition of water to 1- $\beta$ -D-ribofuranosylthieno[3,4-*d*]pyrimidin-4(1*H*)-one **301** at ambient temperature resulted in the ring opening of the pyrimidine ring, to give 4-[(*N*-( $\beta$ -D-ribofuranosyl)formylamino]thiophene-3-carboxamide **386** in quantitative yield (90MI7).



### C. PHYSICOCHEMICAL PROPERTIES

For the thieno[3,4-*d*]pyrimidines the following spectral data are available.

**UV data:** 90M17; 93JHC509.

**IR data:** 81JHC67; 89CPB2091, 89CPB2122, 89CPB2717, 89H985; 90JHC1761, 90LA1215; 92PHA577, 92SC3221.

**<sup>1</sup>H-NMR:** 81JHC67; 88JMC1786, 88TL3537; 89CPB2091, 89CPB2122, 89CPB2717, 89H985; 90JHC1761, 90LA1215, 90MI7; 92SC3221; 93JHC509.

**<sup>13</sup>C-NMR:** 90LA1215, 90MI7; 93JHC509.

**Mass spectral data:** 89H985; 91MI4; 92PHA577.

In addition, *ab initio* Hartree-Fock crystal orbital calculations were performed upon 5,7-dimethylaminothieno[3,4-*d*]pyrimidine (90MI8).

#### D. APPLICATIONS

The following biological properties of thieno[3,4-*d*]pyrimidines have been patented: angiotensin II receptor blocking (93MIP1), antibacterial (87EUP225182), antihypertensive (87USP4670560), antiulcer (90EUP404356), fungicidal (91EUP452002), gastric acid secretion inhibitory (91MIP1), insecticidal and muticidal (91EUP452002), phosphodiesterase inhibitory (89MI6), and vasodilatory (87USP4670560).

Methyl 3,4-dihydro-2-methyl-5-methylthio-4-oxothieno[3,4-*d*]pyrimidine-7-carboxylate **347a** possesses significant antiallergic activity (92PHA577).

Thieno[3,4-*d*]pyrimidine-2(1*H*),4-dione **312** exhibited potent oral antihypertensive activity in spontaneously hypertensive rats (SHR) with a 0.21 mg/kg dose required for reducing systolic blood pressure (SBP) by 50 mm Hg (ED<sub>50</sub>SBP). The ED<sub>50</sub> value is 10.4 mg/kg (88JMC1786).

Thieno[3,4-*d*]pyrimidines with a 4-(4-fluorobenzoyl)piperidine or bis(4-fluorophenyl)methyl-4-piperylidene substituent instead of the 4-phenyl-substituted piperazine group in compounds **306** were twenty times more potent as selective 5-HT<sub>2</sub> antagonists than ketanserin (91MI1).

Several 5-aminothieno[3,4-*d*]pyrimidine-2,4-diones **358** showed phosphodiesterase inhibitory activity superior to that of theophylline (90MI9; 91MI3).

Determination of *in vitro* growth inhibitory activity of several thieno[3,4-*d*]pyrimidine *C*-nucleosides against L1210-C1, sarcoma 180, and HL60 cell lines indicated that 4-amino-7-β-D-ribofuranosylthieno[3,4-*d*]pyrimidine **377** is by far the most cytotoxic, with IC<sub>50</sub> values of 0.0046, 0.015 and 0.0092 μM, respectively (93JHC509).

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# Tropones, Tropolones, and Tropylium Salts with Fused Heterocyclic Rings<sup>1</sup>

## Part 2: Structure, Reactivity, and Application

GUNTHER FISCHER

*Geibelstraße 15, D-04129 Leipzig, Germany*

*Respectfully dedicated to Professor Tetsuo Nozoe—the Nestor of seven-membered ring chemistry*

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<sup>1</sup> Part 1 [*Advan. Heterocycl. Chem.* **64**, 81 (1995)] contains the introductory Section I and the synthetic Section II, including Schemes 1–72 (formulas **1–290**) and Tables I–VIII.



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### III. Structure

#### A. TROPONES AND TROPOLONES

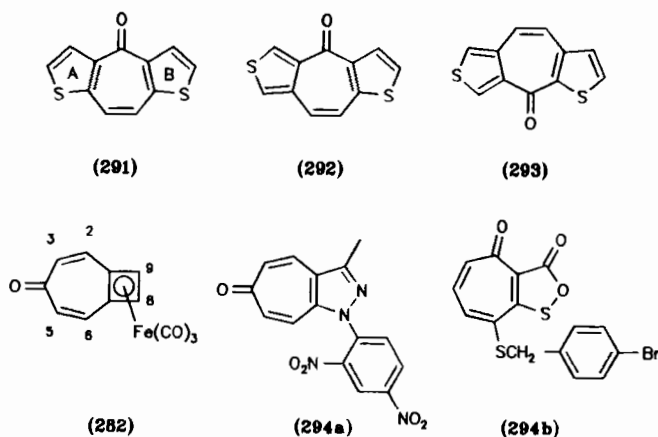
##### 1. *X-Ray Diffraction*

Since 1976, X-ray diffraction studies on heterocyclic fused tropones and tropolones have concentrated on the elucidation of the molecular geometries or chemical structures of relevant synthetic and natural products. Three isomeric dithienotropones **291**–**293** (Scheme 73) studied this way proved to be almost planar [78AX(B)2235, 78CSC389, and 76AX(B)1490, respectively]. Deviations from planarity give them a shallow boat form (**291**, **293**) or a slight chair form (**292**). Conjugation, present in **291**, is indicated by short formal C–C single bonds and long C–O distance.

The crystal structure of pyrazolotropone **294a** has been determined (93MI2; 94TH1). Its phenyl substituent is nearly perpendicular to the plane of the parent rings. Furthermore, benzoxazinotropone **297** (Scheme 74) was found to exist in the solid state in an intermolecularly hydrogen-bonded, dimeric structure. The H bond is located between the carbonyl oxygen in the one molecule and the imine hydrogen in the other (91BCJ2131).

Comparison of the tropone ring geometry in iron complex **282** with that of the parent tropone shows that the double bond character of the carbonyl group and the bond between C-2 and C-3 in **282** is even higher, probably as a result of dominant contributions from two cyclobutadiene resonance

<sup>2</sup> In Part 2, the coverage of publications has been extended to papers reviewed in *Chemical Abstracts* up to Vol. **124** (June 3, 1996). New relevant *synthetic* items are treated within an addendum (Section VI).

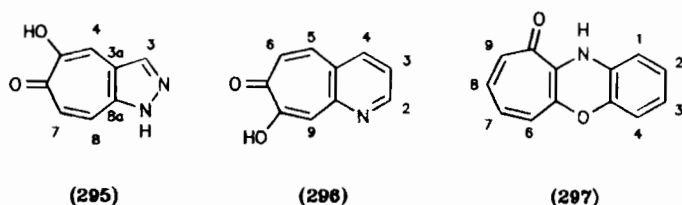


SCHEME 73

forms (78AJC1619). Accordingly, the calculated (VB, HMO) C—C bond order of the C-2—C-3 bond is highest and the bond length is lowest [82JOM(232)163].

In the field of natural products (Section II,A,4), the structures of *S*-(*p*-bromobenzyl)thiotropocin (**294b**; 84TL419), acetyl anhydrocolchicine [83AX(C)1709], and citropone A (**170**; 90CPB1881) have been determined. X-ray analysis has also confirmed the pyrrolotropone structure **53b** (93T113).

Natural ditropolonofuran utahin (**162**) exhibits only approximate planarity, and certain bond-length alternations indicate some double-bond fixation for C—C and C—O bonds [76AX(B)3118]. Each part of the ditropolone is involved in intramolecular hydrogen bonds, but only one part forms intermolecular hydrogen bonds. The latter give dimers of centrosymmetrically related molecules.



SCHEME 74

## 2. Molecular Spectra

a. *<sup>1</sup>H-NMR Spectra.* <sup>1</sup>H-NMR Spectra have become the most important spectrometric tools both for structural elucidation and for investigations of electron density distribution, aromaticity, or tautomerism of fused tropenoids. Whereas monocyclic tropone and tropolone show a broad singlet under usual experimental conditions, chemical shift differences are pronounced in most fused analogs (59MI1, p. 380; 66MI2, p. 132; 73CRV293, p. 326; 84MI2, p. 91; 90MI3, p. 111).

Chemical shifts of various heterocyclic fused parent compounds and some derivatives are listed in Tables IX (for ring structure and numbering, cf. **295**, Scheme 74), X (cf. **296**), and XI (cf. **297**). Furthermore, shift assignments have been reported for four isomeric benzopyridotropones (71JHC73), pentacyclic tropone **276** [89H(29)1005], antibiotic thiotropocin derivative **294b** (92JA8479), ferrocenotropone and -tropolone (69BSF1182), and tricarbonyliron cyclobutadiene-fused tropones **287** (70JA6382) and **282** (77JA513; 78AJC1607).

Jin and Li (92MI3) recently compared the NMR data of pyrazolo- and isoxazolotropones, deriving the chemical shifts from the electron delocalization. By means of characteristic NMR spectra, isomeric structures can be assigned, for example, in the case of **98b** (91JHC717) or **295** (Table IX; 72JHC967). The interpretation of the NMR spectra is facilitated by deuteration of OH- and NH-acidic functionalities [82IJC(B)765] or by synthetically exchanging nuclear CH for CD groups [70CR(C)551; 74BSF(2)1383].

The site of *N*-alkylation in pyrazolotropones **143a,b** (72TL1925) and imidazotropones **185** and **186** (92JHC1219) was elucidated by the lanthanide-induced shift reagents Eu (dpm)<sub>3</sub> and Eu (fod)<sub>3</sub>, respectively. Likewise, Pr (dpm)<sub>3</sub> was used [93JCS(P1)1617].

The coupling constants of pyrazolotropone **143a** are very similar to those reported for tropone and simple derivatives as well as such fused derivatives as **6a** and **100** (Table IX) or **282**.

Certain protons of fused troponoids show remarkable low-field shifts (Table XII, Scheme 75; for comparison, see Tables IX and X). These protons are abnormally deshielded by the paramagnetic anisotropy effect of *peri*-positioned or other neighboring groups, especially the tropone carbonyl groups. Similar low-field shifts are caused by adjacent nitro or halogen substituents [e.g., 74YZ1445; 80JCS(P1)2081].

The methine proton of the isopropyl group in pyrrolotropone **299a**<sup>3</sup> also appears at an unusually low field (80BCJ3373). Moreover, its signal is a

<sup>3</sup> In the formula schemes, substituents (R) or ring atoms (Z) in parentheses refer, in the range given, to substructures **a**, **b**, **c**, etc.

TABLE IX  
<sup>1</sup>H-NMR CHEMICAL SHIFTS OF TROPONIDS WITH FUSED FIVE-MEMBERED HETEROCYCLIC RINGS (TYPE 295)

Fused heterocycle <sup>a</sup>	Positions of		Further substitution	Formula no.	$\delta$ (ppm) <sup>b</sup> in positions								Solvent	Reference
	CO	OH			1	2	3	4	5	6	7	8		
[b]furan	4	—	—	<b>6a<sup>c</sup></b>	—	7.7	7.22	—	7.15	7.25	6.85	7.48	CDCl <sub>3</sub>	73JCS(P1)968
[b]thiophene	4	—	—	<b>51</b>	—	7.78	7.92	—	7.48	7.06	6.23	6.99	CDCl <sub>3</sub>	73JA6655
[b]pyrrole	4	—	2-Ph	—	10.47	—	6.79	—	7.60	7.67	7.49	8.41	CDCl <sub>3</sub>	93H(36)2247
pyrazole	4	—	1-Me	<b>143a</b>	(3.33)	—	7.90	—	6.7	6.6	6.2	7.3		72TL1925
[b]furan	6	—	—	<b>306a</b>	—	7.61	6.77	7.50	6.80	—	6.80	7.50	<i>e</i>	74BSF(2)1383
[c]furan	6	—	—	<b>307a</b>	7.83	—	7.83	7.16	6.35	—	6.35	7.16	<i>e</i>	
[b]thiophene	6	—	—	<b>306b</b>	—	7.52	7.30	7.55	6.85	—	6.85	7.55	<i>e</i>	71BSF1437
		5	—	<b>308b</b>	—	8.07	7.55	7.75	—	—	7.05	8.12	<i>e</i>	
		7	—	<b>309b</b>	—	7.77	7.52	7.98	7.09	—	—	7.85	<i>e</i>	
[c]thiophene	6	—	—	<b>307b</b>	7.67	—	7.67	7.29	6.37	—	6.37	7.29	<i>e</i>	
		5	—	<b>310b</b>	8.40	—	8.08	7.46	—	—	6.73	7.87	<i>e</i>	
[b]pyrrole	6	—	1-Me	—	(3.85)	7.00	6.54	7.48	6.78	—	6.78	7.40	CDCl <sub>3</sub>	73JHC1083
[c]pyrrole	6	—	2-Me	<b>529a</b>	7.02	(3.78)	7.02	7.25	6.39	—	6.39	7.25	CDCl <sub>3</sub>	85T3303
pyrazole	6	—	—	<b>323</b>	—	—	7.80	6.90	6.40	—	6.64	7.60	DMSO-d <sub>6</sub>	72JOC676
		5	—	<b>295</b>	—	—	8.20	7.44	—	—	6.68	7.96	DMSO-d <sub>6</sub>	72JHC967
imidazole	6	—	1-Me	—	(3.86)	7.78	—	7.68	6.92	—	6.92	7.37	DMSO-d <sub>6</sub>	83JPR853
[b]furan	8	—	2-Me	<b>100<sup>d</sup></b>	—	(1.98)	6.00	6.91	6.44	6.73	7.18	—	C <sub>6</sub> D <sub>6</sub>	74HCA1598
pyrazole	8	—	3-Me	<b>85</b>	—	—	(2.62)	7.59	6.87	7.45	7.19	—	CDCl <sub>3</sub>	92CPB1606
[d]isoxazole	8	—	3-Me-5-NO <sub>2</sub>	—	—	—	(2.71)	8.61	—	8.38	7.39	—	CDCl <sub>3</sub>	87JHC779
oxazole	8	—	7-Br	—	—	8.24	—	8.32	6.97	7.72	—	—	CDCl <sub>3</sub>	88JHC285
thiolzole	8	—	2-SMe	<b>485a</b>	—	(2.78)	—	7.74	7.04	7.29	7.08	—	CDCl <sub>3</sub>	95PS(101)167

<sup>a</sup> [b]-, [c]-, and [d]-fusion as given in formulas **306b**, **307b**, and **327** (Schemes 77 and 84), respectively. <sup>b</sup> Figures in parentheses refer to methyl groups.

<sup>c</sup> Coupling constants (Hz):  $J_{23} = 2$ ;  $J_{56} = 12$ ;  $J_{57} = 1.5$ ;  $J_{67} = 8$ ;  $J_{68} = 1$ ;  $J_{78} = 11$ . <sup>d</sup> Coupling constants (Hz):  $J_{45} = 10.5$ ;  $J_{46} = 1.2$ ;  $J_{47} = 1.2$ ;  $J_{56} = 8.4$ ;  $J_{57} = 0.9$ ;  $J_{67} = 12.2$ ;  $J_{3,Me} = 0.9$ . <sup>e</sup> Deuterated solvent.

TABLE X  
<sup>1</sup>H-NMR CHEMICAL SHIFTS OF TROPONIDS WITH FUSED SIX-MEMBERED HETEROCYCLIC RINGS (TYPE **296**)

Fused heterocycle <sup>a</sup>	Positions of		Further substitution	Formula no.	$\delta$ (ppm) <sup>b,c</sup> in positions									Reference
	CO	OH			1	2	3	4	5	6	7	8	9	
[c]pyran	7	6	9-OH-3-Me	<b>169</b>	5.00	—	(1.87)	5.49	6.20	—	—	6.58	—	65CJC1835
[b]pyridine	5	—	9-Br	—	—	9.06	7.6	8.6	—	6.95	6.95	7.76	—	84JCS(P1)2297
	7	8	—	<b>296</b>	—	8.93	7.42	8.06	7.76	7.23	—	—	7.93	70BSF3636
[c]pyridine	5	—	—	—	9.05	—	8.83	8.24	—	7.19	7.19	6.88	7.39	84JCS(P1)2297
	7	6	—	—	9.15	—	8.82	7.6	7.52	—	—	7.35	8.0	70CR(C)551
	9	—	—	<b>356</b>	9.57	—	8.84	7.45	7.22	6.87	7.03	7.03	—	84JCS(P1)2297
pyrimidine	9	—	2-NH <sub>2</sub> -4,6-di-Me	—	—	—	—	{2.63}	7.57	(2.43)	···	7.28	···	92JHC795
benchrotrene <sup>d</sup>	7	—	6,8-di-Me	—	·····	5.49	·····	·····	7.00	(2.22)	—	(2.22)	7.00	74CR(C)1117

<sup>a</sup> [b]- and [c]-fusion as given in formulas **296** and **356** (Schemes 74 and 94), respectively. <sup>b</sup> Shifts in parentheses refer to methyl groups; shifts among dotted lines represent unresolved peaks common to more than one H atom. <sup>c</sup> Solvent CDCl<sub>3</sub>, except substance **169** (D<sub>2</sub>O). <sup>d</sup> Benzene chromium tricarbonyl.

TABLE XI  
<sup>1</sup>H-NMR CHEMICAL SHIFTS OF QUINOLINO- AND BENZAZINOTROPONES (TYPE **297**)

Fused system	Position of CO	Further substitution	Formula no.	$\delta$ (ppm) <sup>a,b</sup> in positions											Reference
				1	2	3	4	5	6	7	8	9	10	11	
quinoline	8	7,9-bis-COOEt-3-Me	—	7.84	7.51	(2.60)	7.95	—	8.38	—	—	—	8.16	8.48	81JCS(P1)2509
quinoxaline	10	7,9-di-Br-5-Me	<b>118c</b>	6.37	6.62	6.74	6.24	(2.94)	6.49	—	7.69	—	—	—	89H(29)1459
benzoxazine	6	—	<b>267</b>	6.56	6.64	6.72	6.42	—	—	6.49	.....	6.81...	....	—	91BCJ2131
	7	—	—	6.84	6.75	6.89	6.70	—	6.33	—	6.13	6.81	5.99	—	
	8	—	—	6.52	6.73	6.64	6.43	—	6.75	6.36	—	...6.69...	—	—	
	9	—	<b>22</b>	6.83	6.78	6.88	6.71	—	6.39	6.70	6.32	—	6.05	—	
	10	—	<b>297</b>	6.93	6.73	6.68	6.57	—	6.78	6.68	7.03	6.94	—	—	
benzothiazine	10	—	<b>361</b>	...6.45–6.50...			5.74	—	6.22	5.84	6.25	6.99	—	—	85BCJ165

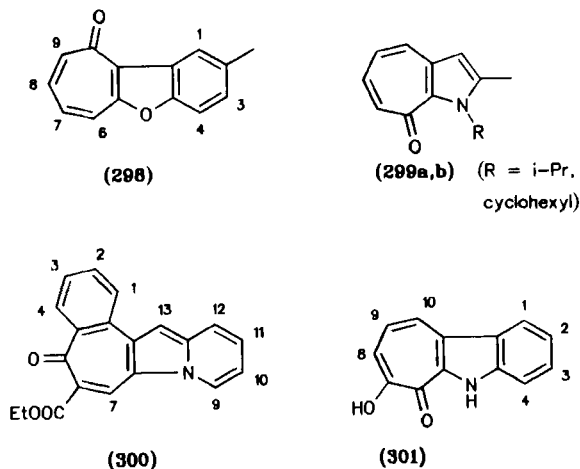
<sup>a</sup> See Table X, Footnote (b). <sup>b</sup> Solvents: DMSO-d<sub>6</sub> (benzoxazines), benzene (benzothiazine), or CDCl<sub>3</sub>.

TABLE XII  
CHARACTERISTIC LOW-FIELD SHIFTS IN  $^1\text{H}$ -NMR SPECTRA OF FUSED TROPONIDS

Fused heterocycle	Formula no.	Deshielding		Deshielded		Reference
		Group	(Position)	Proton	( $\delta$ )	
benzofuran	<b>298</b>	CO	(10)	H-1	(8.5)	66JCS(C)926
[c]pyridine	—	CO	(5)	H-4	(8.24)	84JCS(P1)2297
	<b>356</b>	CO	(9)	H-1	(9.57)	
cycloheptapyrrole	<b>646</b>	CO	(1)	H-11	(10.50)	94JCS(P1)2579
pyrazole	<b>86a</b>	CO	(8)	Me at N-1	(4.39) <sup>a</sup>	80BCJ1461
	<b>142<sup>b</sup></b>	CO	(8)	Me at N-1	(4.47)	66BCJ253
oxazole	<b>114a</b>	tropone		H-2	(8.21)	84BCJ609
[b]furan	<b>171</b>	CO	(3-Ac)	H-4	(8.37)	76TL2339
[b]pyridine	—	OMe	(5)	H-4	(8.45)	90JOC3341
	—	OMe	(6)	H-7	(8.09)	
	<b>443</b>	N <sup>+</sup> —O <sup>-</sup>	(1)	H-9	(8.72)	70BSF3636
[b]furan	—	—O—	(1)	H-8		79MI2
[b]pyrrole	<b>299a</b>	CO	(8)	H-iPr	(6.33)	80BCJ3373

<sup>a</sup> Isomeric 2-Me compound (**87a**):  $\delta$  4.05. <sup>b</sup> H-3  $\delta$  8.08; isomeric 4-oxo compound: N-Me  $\delta$  4.15, H-3  $\delta$  8.46.

broad unresolved peak ( $\delta$  6.33) at room temperature, but becomes a sharp septet at 80°C. However, at -80°C the spectrum indicates the presence of rotamers by showing pairs of signals in a ratio of about 1:2. The methine group of 1-cyclohexyl derivative **299b** behaves similarly.



SCHEME 75

Pentacyclic pyrrolotropones such as **53b** exhibit characteristic doublet signals for the vinylic  $\alpha$ -protons (H-13) of the tropone enone systems around  $\delta = 6.9$  ppm (93T113), thereby confirming the structure. In indolizinobenzotropones such as **300**, typical low-field singlets ( $\delta$  8.49) appear for the H-7 protons [84H(22)791].

The spectrum of pyrazolotropone **143d** exhibits a complex multiplet between  $\delta$  6.5 and 7.2 (78JOC817). The similarity of these resonances, together with their downfield position with respect to relevant protons in  $\alpha$ ,  $\beta$ -unsaturated ketones, reflects the aromatic character of **143d**.

In oxepino- and azepinotropones **156**, the vicinal proton coupling constants are comparable to those of the monocyclic constituents. Thus,  $^1\text{H}$ -NMR spectroscopy reveals that the heterocyclic rings maintain a boat conformation while the tropone moieties remain almost planar (88CL1647; 90CL91).

In oxepinotropone **147b**, the heteroring protons (H-2–H-5) appear at a lower field than those in 1-benzoxepine. In the tropone ring, the  $\alpha$ -protons (H-7, H-9) resonate at low field while the  $\beta$ -protons (H-6, H-10) are observed at higher field than those of benzo[*d*]tropone [94H(38)957].

The low-field position of the OH resonance of the parent tropolone ( $\delta$  9.51) strongly indicates an intramolecularly hydrogen-bonded structure (73CRV293, p. 331). Likewise, in indolotropolone **301** an H-bond (OH:  $\delta$  10.03) is found to be directed from OH to CO, but not from NH to CO [70JPR(312)466]. Generally, the proton signals of tropolones fused to five-membered rings (Table IX) appear at lower field than those of the corresponding tropones.

Furthermore,  $^1\text{H}$ -NMR spectra were used to determine the isomerization of troponofuroxan **326** (Section III,A,4,c; 74JOC2956) and to detect tropylium ion structures in solutions of certain tropones in strong acids (Section II,C,1,d).

b.  *$^{13}\text{C}$ -NMR Spectra.*  $^{13}\text{C}$ -NMR spectra of used troponoids have been published since 1978; some relevant examples are shown in Table XIII (cf. Schemes 74 and 76).

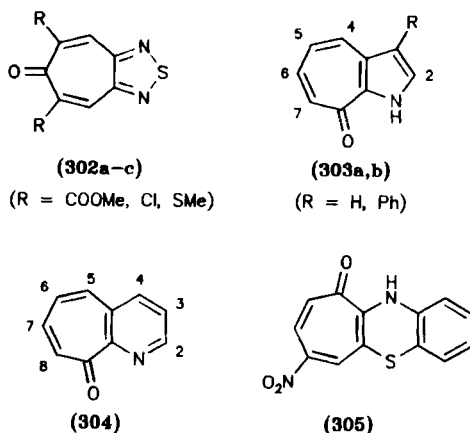
These spectra have been used for the structural elucidation of natural and synthetic products such as citropone alkaloid **170** (90CPB1881), antibiotic thiotropocin **168** (84TL419) and its *p*-bromobenzyl thioether **294b** (92JA8479), and pentacyclic furotropone **53a** (92T5481). A comparison of the spectrum of the tropone-fused tricarbonyliron cyclobutadiene **282** with the spectra of the two monocyclic constituents shows that the formal fusion does not result in large changes in chemical shifts (78AJC1607).



TABLE XIII  
<sup>13</sup>C-NMR CHEMICAL SHIFTS OF TROPONES WITH FUSED HETEROCYCLIC RINGS

Fused heterocycle	Position of CO <sup>a</sup>	Further substitution <sup>a</sup>	Formula no.	$\delta$ (ppm) <sup>b</sup> in positions <sup>a</sup>										Reference
				1	2	3	3a	4	5	6	7	8	8a	
[c]furan	6	—	<b>307a</b>	144.6	—	144.6	123.6	129.4	131.5	190.2	131.5	129.4	123.6	94TL8421
[b]thiophene	6	5,7-di-Ph	<b>518a</b>	—	128.5	131.6	—	132.5	—	187.2	—	130.6	—	86CJC1360
[c]pyrrole	6	2-Bu-1, 3-di-Me	<b>264c</b>	128.9	—	128.9	118.7	132.2	125.9	189.9	125.9	132.2	118.7	79CB2087
pyrazole	6	1-(2,4-di-NO <sub>2</sub> -Ph)-3-Me	<b>294a</b>	—	—	150.9	121.8	130.7	132.4	186.7	137.0	123.2	141.2	94TH1
[2,1,3]thiadiazole	6	5,7-di-COOMe	<b>302a</b>	—	—	—	155.9	130.9	136.7	183.5	136.7	130.9	155.9	82CZ411
		5,7-di-Cl	<b>302b</b>	—	—	—	153.9	129.1	140.9	173.4	140.9	129.1	153.9	
		5,7-di-SMe	<b>302c</b>	—	—	—	153.9	120.4	147.5	180.2	147.5	120.2	153.9	
[b]thiophene	8	2-Me	<b>65</b>	—	141.5	127.5	148.6	132.6	129.7	135.9	134.3	180.5	150.1	83H(20)1709
		2-Me-4- <i>i</i> Pr	—	—	141.2	123.3	147.9	152.3	126.6	136.0	131.8	180.4	151.8	
		2-Me-5- <i>i</i> Pr	<b>458b</b>	—	142.1	128.5	148.3	130.0	148.0	137.4	134.2	179.8	147.6	
		2-Me-6- <i>i</i> Pr	—	—	141.0	129.3	148.1	131.3	129.5	156.5	131.3	179.9	149.6	
		2-Me-5-OMe	—	—	141.0	129.3	149.0	107.3	158.3	133.7	133.9	179.0	149.0	
pyrazole	8	3-Me	<b>85</b>	—	—	150.2	121.9	130.3	123.7	138.5	134.3	176.8	143.9	92CPB1606
thiazole	8	2-SMe	<b>485a</b>	—	179.1	—	153.8	132.8	129.6	136.0	136.2	175.0	140.7	95PS(101)167

<sup>a</sup> Numbering according to formula **295**. <sup>b</sup> In CDCl<sub>3</sub> except for tropone **294a** (DMSO-d<sub>6</sub>).



SCHEME 76

c. *Electronic Spectra.* In early studies especially, UV-vis spectra were used to characterize the compounds under review. Even today they are useful tools for structural assignments, differentiating between isomers, and for investigations on tautomerism or aromaticity.

The UV spectra of monocyclic tropones and tropolones can generally be divided into region A (about 200–300 nm;  $\log \epsilon$  4.0–4.7) and region B (about 300–400 nm;  $\log \epsilon$  3.0–4.0) [55CRV9, p. 19; 56FOR(13)232, p. 263; 59MI1, p. 371; 73CRV293, p. 327]. Region B can be further divided (56MI2, p. 319) into subregions B<sub>1</sub> (about 300–350 nm) and B<sub>2</sub> (350–400 nm). The higher-wavelength band is characteristic for tropolones and 2-amino- or 2-mercaptotropones (cf. Table XIV, first entries). This band is caused by intramolecular hydrogen bonding and changes markedly with solvent and pH value.

Many fused tropones show typical absorptions of tropone itself (73CRV293, p. 329). Considerable differences are often observed in the longwave region of tropones and tropolones (e.g., 65BCJ301). UV data of typical heterocyclic troponoids are listed in Tables XIV–XVI (cf. Scheme 76).

Compared with monocyclic compounds the heterocyclic analogs—as shown by nearly every example given in Tables XIV and XV—exhibit a *bathochromic shift* induced by annulation (73CRV293, p. 332). Often, the absorption extends into the visible region. The same is true, for instance, for yellow or orange pyrrolo- and pyronotropones such as **181** and **78** (65BCJ306; 91JHC817), pyranotropolone **169** (65CJC1835), pyrazolotropo-

TABLE XIV  
UV MAXIMA OF TROPONIDS WITH FUSED FIVE-MEMBERED HETEROCYCLIC RINGS (TYPE 303)

Fused ring <sup>a</sup>	Positions of		Further substitution	Formula no.	$\lambda_{\max}$ in nm (log $\epsilon$ )					Solvent <sup>b</sup>	Reference
	CO	OH			Region A		Region B				
— <sup>c</sup>	1	—	—	—	225	(4.34)				IO	59MII, p. 374
— <sup>d</sup>	1	2	—	—	297	(3.74)	310	(3.67)			
					222	(4.37)	232	(4.36)	238	(4.37)	CH
					322	(3.84)	340	(3.64)	(B <sub>1</sub> )		
					356	(3.73)	374	(3.74)	(B <sub>2</sub> )		
benzene <sup>e</sup>	7	—	—	—	234	(4.53)	265	(4.52)			CH
					326	(3.37)	341	(3.10)			
[b]furan	4	—	—	<b>6a</b>	220	(4.42)	260	(3.86)			
					312	(3.93)	342	(3.94)	356	(3.93)	
	8	—	2-Me	<b>100</b>	264	(4.43)	271	(4.43)	300	(3.86)	EtOH
					338	(3.58)					
[c]furan	6	—	—	<b>307a</b>	211	(4.08)	216	(4.05)	250	(4.57)	EtOH
					292	(3.67)	301	(3.67)			
[b]thiophene	4	—	—	<b>51</b>	238	(4.33)	241	(4.34)			
					324	(3.94)	346	(3.89)	360	(3.84)	
	8	—	2-Me	<b>65</b>	243	(4.25)	290	(4.22)			MeOH
					349	(3.54)	364	(3.30)			
[c]thiophene	6	—	1,3-di-Me	<b>393</b>	228	(4.14)	276	(4.63)			EtOH
					331	(4.01)					

[b]pyrrole	4	—	1-Me	<b>319</b>	239 (4.48)	247 (4.48)					80JCS(P1)2081]
					312 (4.03)	373 (3.96)					
	8	—	—	<b>303a</b>	232 (4.44)	270 (4.37)			EtOH	61YZ1799	
					356 (3.76)	374 (3.70)					
[c]pyrrole	6	—	1,3-di-Me-2-Ph	<b>315c</b>	293 (4.74)	328 (4.06)	343 (3.96)		EtOH	69ZOR570	
					386 (3.40)						
imidazole	6	—	2-OEt	<b>19</b>	246 (4.37)				EtOH	68CPB1308	
					350 (4.37)						
	6	5	—	<b>133</b>	250 (4.44)	268 (4.28)	280 (4.14)		MeOH	61BCJ1410	
					372 (4.14)						
	8	—	2-Me	<b>105a</b>	243 (4.45)	290 (3.73)	301 (3.80)		EtOH	69MI1	
					335 (3.73)	350 (3.80)	368 (3.60)				
triazole	6	5	—	<b>134</b>	229 (4.52)	259 (4.12)	269 (4.04)		MeOH	70TL1725	
					345 (4.04)						
[c]isoxazole	8	—	3-Me	<b>91</b>	220 (4.52)	277 (3.86)			MeOH	82JHC525	
					374 (3.91)						
[d]isoxazole	8	—	3-Me	<b>90</b>	232 (4.34)				MeOH	82JHC525	
					329 (3.97)	340 (3.96)					
oxazole <sup>f</sup>	8	—	2-Me	<b>114b</b>	242 (4.42)				MeOH	56MI1	
					310 (3.76)						

<sup>a</sup> See Table IX, Footnote (a). <sup>b</sup> IO = isooctane, CH = cyclohexane. <sup>c,d</sup> Parent tropone and tropolone, respectively. <sup>e</sup> Benzo[d]tropone (numbered like type **304**). <sup>f</sup> Quaternary salt (2,3-dimethyl-8-oxocycloheptoxazolium perchlorate, **507**; 63UP2):  $\lambda_{\max}(\log \epsilon)$  243 (4.28) and 333 (3.93), region A; 492 (2.62), region B.

TABLE XV  
UV MAXIMA OF PYRIDOTROPONES AND -TROPOLONES (TYPE **304**)

Fusion <sup>a</sup>	Positions of		Further substitution	Formula no.	$\lambda_{\max}$ in nm (log $\varepsilon$ )					Solvent	Reference	
	CO	OH			Region A Region B							
[b]	5	—	—	—	218	(4.52)	240	(4.16)	248	(4.15)	EtOH	84JCS(P1)2297
					303	(3.72)	340	(3.78)	351	(3.73)		
	7	6	2-Me	—	250	(4.58)	356	(3.85)	430	(3.02)	MeOH	59MI4
					320	(3.70)						
		—	6-Cl	—	242	(4.50)					MeOH	77TL2663
					319	(3.79)						
	8	—	<b>296</b>	230	(4.54)	268	(4.39)	MeOH	59MI4			
				343	(4.06)	372	(4.04)			378	(4.02)	
	9	—	—	<b>304</b>	220	(4.57)	EtOH	73JCS(P1)968				
					338	(4.20)						
[c]	5	—	—	—	217	(4.45)	325	(3.98)	348	(3.84)	EtOH	84JCS(P1)2297
					312	(3.98)						
	9	—	—	<b>356</b>	214	(4.36)					EtOH	
					315	(3.83)						

<sup>a</sup> See Table X, Footnote (a).

TABLE XVI

UV VIS MAXIMA OF INDOLO- AND BENZAZINOTROPONES (TYPES **301** AND **297**, RESPECTIVELY)

Fused system	Position of CO	Formula no.	$\lambda_{\max}$ in nm (log $\epsilon$ ) <sup>a</sup>						Reference
indole	6	<b>(56b)</b>	224	(4.47)	276	(4.46)	309	(4.30)	75CPB2818
			336	(4.17)	383	(3.92)	403	(4.03)	
	10	<b>(56a)</b>	218	(4.55)	237	(4.42)	281	(4.37)	
quinoxaline	8	<b>27</b>	376	(4.01)	396	(3.91)			58MI2
			225	(4.32)	278	(4.59)			
benzoxazine	6	<b>267</b>	375	(4.08)	395	(4.01)			83BCJ2756
			205	(4.40)	228	(4.34)	260	(4.20)	
	7	—	292	(4.10)	400	(3.88)			91BCJ2131
			221	(4.27)	237	(4.14)	295	(4.29)	
	8	—	427	(4.02)					
			222	(4.12)	266	(4.34)	275	(4.32)	
	9	<b>22</b>	420	(4.02)					
			239	(4.19)	307	(4.55)			
	10	<b>297</b>	373	(3.77)	394	(3.77)			83BCJ2756
			205	(4.24)	227	(4.28)	259	(4.21)	
benzothiazine	6	<b>123</b>	270	(4.21)	284	(4.05)	483	(3.88)	66BCJ1980
			230	(4.32)	285	(4.35)			
	8	<b>136</b>	425	(3.71)					
			225	(4.24)	275	(4.25)	330	(3.69)	
	10	<b>361</b>	418	(3.70)					61BCJ146
			233	(4.36)	285	(4.33)			
			440	(3.82)					

<sup>a</sup> Solvents: methanol or (**56a,b**) ethanol.

lone **81a** (66BCJ253), oxepinotropone **156a** or its  $\beta$ -cyclodextrin inclusion complex [88CL1647, 88SA(A)1227], and cyclohepta[c]furan-6-ones and their thiophene (**315a,b**; cf. Scheme 79) or pyrrole analogs (67JOC1610; 83AP730; 87AP362).

Besides the colored indolo- and benzazinotropones listed in Table XVI, analogous substances have been described by Mühlstädt *et al.* [57LA(608)38; 70JPR(312)466] and Nozoe *et al.* (75BCJ314; 78BCJ3316; 89BCJ128). Among the five isomeric benzoxazine derivatives (Table XVI; 91BCJ2131), the red 10-keto compound **297** shows its highest-wavelength band centered at 483 nm. Theoretical calculations prove that the latter compound exists in a dimeric, hydrogen-bonded structure (Section III,A,1) while its four isomers maintain the normal keto form.

Further examples of extended conjugation of the chromophores are exhibited by heterocyclic bitropenoids (61BCJ151; 82CL701; 85CBJ515), tricyclic tropones [80BCJ1406; 94JCS(P1)2579], tetracyclic tropenoids

[78BCJ3579; 84H(22)791], pentacyclic tropones [89H(29)1005], and iron complexes **282** and **287** (78AJC1607 and 70JA6382, respectively).

The comparison of thienotropones like **226a** with pyrrolotropones like **226b** reveals a new longwave band at about 400 nm in the spectra of the latter and bathochromic shifts of other bands (68ZOR907).

Bathochromic shifts are also caused by certain substituents at the seven-membered rings, especially by bromine [62BCJ349, 62BCJ808; 65BCJ301; 80JCS(P1)2081; 85BCJ2840] and other halogens, methyl (69ZOR570), nitro (62BCJ808), and amino groups [81H(16)935], but not by halogen at the heterocyclic rings (61YZ1799; 62YZ418; 63CPB1440; 67JOC1610).

Shifts can reach high values. In benzothiazinotropone **361** (Table XVI) one additional nitro group at C-7 shifts the longest-wave maximum from 440 up to 553 nm; nitro product **305** is described as "black needles" (66BCJ1980). However, steric hindrance can influence the shift of the  $\lambda_{\max}$  values. Whereas in similar derivatives **448a** and **449a** (see Scheme 123) one nitro group at C-9 shifts the maximum by about 40 nm to larger wavelengths, in the corresponding 8-isopropyl-substituted homologs (**448b**, **449b**) the shift amounts to just 13 nm (66BCJ1988).

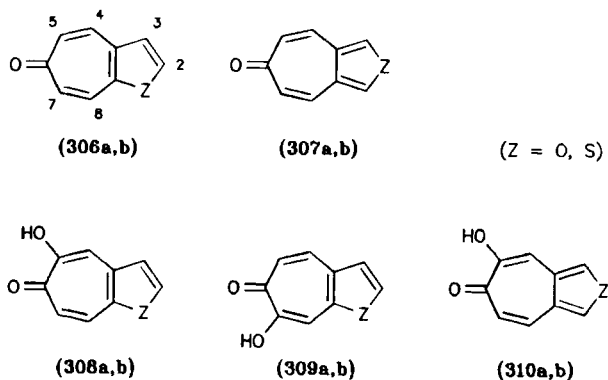
Bathochromic effects can also arise from substituents at the heterorings, for example, from 2-amino or 2-hydroxy groups of imidazotropones **15** and **16** (62BCJ1188) or furotropone **173** (91M12).

*Solvent effects* on UV spectra are quite variable in the field of fused troponoids. Whereas the spectra of imidazotropone **105a** recorded in cyclohexane and in ethanol are nearly identical (69M11), those of furotropone **104a** (71T6023) and of oxepinotropone **156a** (88CL1647) depend more or less strongly on solvent polarity. Bathochromic shifts were observed in more polar solvents, especially in the longwave region.

Bathochromic effects with increasing *pH value* are observed in the electronic spectra of tropolones and tropones bearing other acidic groups. These effects facilitated structural studies of tropolone **83** (65BCJ362),  $\delta$ -hydroxytropone derivative thiotropocin **168** (84M11), enolizable tropones such as imidazole derivatives **15** and **16** (62BCJ1188), and tropones fused to acidic heterocyclic systems such as pyrazole **183** [82IJC(B)765] and benzothiazine *S*-oxides **448a** and **449a** (see Scheme 121; 66BCJ1988).

El Borai *et al.* [82AC(R)191] tabulated pH-dependent spectral data of furo- (**308a**–**310a**) and thienotropolones (**308b**–**310b**, Scheme 77). The mean bathochromic shift from neutral forms (at pH 3) to anions (at pH 11) amounts to 10 nm.

However, the electronic spectrum of dark green bi(cyclohepta)pyrrole **262** dissolved in tetrafluoboric acid shifts hypsochromically to become, ultimately, identical with the spectrum of tropylium salt **263** (75TL1849). A strong shift in the same direction is observed with acidified

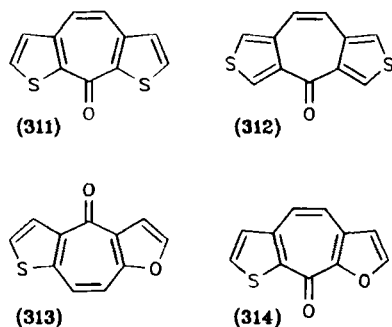


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2-mercaptotroponone due to tautomerization (64BCJ1526), whereas decreasing (or increasing) pH values scarcely influence the spectrum of benzoxazotropone **297** (83BCJ2756). Finally, the spectra of benzothiazotropones **123** and **136** on acidification shift to higher wavelengths (66BCJ1980).

Perben *et al.* (75JHC913) calculated the electronic spectra of thieno[*b*]tropone (**306b**) and -tropolones (**308b**, **309b**) and the corresponding [*c*]-fused isomers (**307b**, **310b**) by CNDO/S formalism. Furthermore, Liljefors *et al.* (73ACS2485) computed within the PPP approximation the spectra of isomeric dithienotropones **291** and **311** and isomeric furothienotropones **313** and **314** (Scheme 78). In both cases the results obtained account satisfactorily for experimental data.

Greco *et al.* (72JHC967, 72JOC676) attribute the UV-absorption bands of pyrazolotropolone **295** and corresponding tropone **323** (see Scheme 82)



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to the pyrazole ring, the tropolone (or tropone) ring, and the conjugated ring carbonyl group.

More recently, Jin (92MI2) investigated several mono- and dimethylated cycloheptazol-8-ones. The similarity of the electronic spectra of pyrazolo-tropones **85**, **86a**, and **87a** is explained by the very similar 10- $\pi$  systems present. However, the spectra of isoxazoles **90** and **91** and of oxazole **114b** are different from those of the pyrazoles. This difference was attributed to the small contribution of the oxygen-atom lone-pair electrons to the conjugation, which minimizes the contribution of the 10- $\pi$  system.

d. *Infrared Spectra.* Early assignments of tropone IR bands [55CRV9, p. 21; 56FOR(13)232, p. 265; 59MI1, p. 373] in later papers had to be revised in some details regarding C=O and C=C stretching frequencies. For tropone and most aromatic-fused tropones, the C=O stretching bands were found to lie at wave numbers lower than that of C=C (61HCA387; 66MI2, p. 131; 73CRV293, p. 326). Their exceptionally low values have been regarded as being due to conjugation, polarity, and ring strain. It is possible to distinguish between C=O and C=C bands because, on changing to more polar solvents, the C=O bands shift to lower wave numbers more strongly than the C=C bands.

In principle, fused tropones behave similarly to their monocyclic analogs (73CRV293, p. 329). IR spectra could be used, for instance, to identify isomeric anhydrosepedonin dimethyl ethers **418a-c** (Scheme 112; 69MI3) and pyrazolotropones substituted at N-1 (**98b**) or N-2 (91JHC717). Table XVII contains selected IR data of relevant compounds as assigned by the respective authors.

Generally, the *carbonyl stretching bands* are found in the region from about 1645 down to 1590  $\text{cm}^{-1}$ . Distinctly higher values extend up to 1664  $\text{cm}^{-1}$  in the case of benzopyridotropones (71JHC73), up to 1675  $\text{cm}^{-1}$  in quinolinotropones [81JCS(P1)2509], and up to 1680  $\text{cm}^{-1}$  in certain tetracyclic dibenzo-fused derivatives [67LA(705)169; 71CB1573; 78IJC(B)567].

However, unusually low values reach down to 1558  $\text{cm}^{-1}$  in the case of cyclohepta[c]pyrrol-6-ones (e.g., **226b** and **315c**, Schemes 55 and 79) and their furan and thiophene analogs (68ZOR907; 69ZOR570; 83AP730; 85T3303) and even to 1540  $\text{cm}^{-1}$  in benzo-fused thieno- and selenophenotropones **234b,c** [83CS(22)53, 83T819] and in tautomerizable thiazolotropone **192** (64BCJ1526).

In the series of dithienotropones, according to Gronowitz *et al.* (73ACS2257; 78JHC285), [*b,b'*]-fused compounds **291** and **311** show C=O bands at lower values (50  $\text{cm}^{-1}$ ) than those of the corresponding dihydro derivatives. This is due to the high contribution of dipolar resonance forms having CO single-bond character. Similar shifts are observed in [*b,c'*]-fused

TABLE XVII  
IR BANDS OF TROPONES AND TROPOLONES WITH FUSED HETEROCYCLIC RINGS

Fused system	Positions <sup>a</sup> of		Further substituents	Formula no.	Tropone ring <sup>b</sup>				Heteroring <sup>b</sup>		Reference
	CO	OH			C=O	C=C	CH	OH	NH	C=N	
[c]thiophene	6	—	1,3-di-Me	<b>393</b>	1590	1617, 1623					69ZOR570
[c]pyrrole	6	—	1,3-di-Me-2-Ph	<b>315c</b>	1577	1597, 1612					
indole	6	—	—	<b>(56b)</b>	1614				3195		76BCJ1101
		7	—	<b>301</b>	1615			...3230... <sup>c</sup>			70JPR(312)466
pyrazole	6	—	5,7-di-Me	<b>406</b>	1592	1610			3205	1515	72JCS(P1)1623
		5	—	<b>295</b>	1592	1634		...3175... <sup>c</sup>			72JHC967
	8	—	3-Me	<b>85</b>	1580				3200		79BCJ1972
imidazole	8	—	1-Ph-3-styryl	<b>79b</b>	1634					1595	89JHC371
			—	<b>188</b>	1620				3350		90JHC887
[d]isoxazole	8	—	3-styryl	<b>79a</b>	1630					1621	89JHC371
oxazole	6	7	4-CH <sub>2</sub> COOH-2-Me	—	1618			3150			61DOK(141)1380
[2,1,3]thiadiazole	6	—	5,7-di-Cl	<b>302b</b>	1635		3040				82CZ411
benzoxazine	6	—	—	<b>267</b>	1640				3240		83BCJ2756
	10	—	—	<b>297</b>	1605				3230		
benzothiazine	10	—	—	<b>361</b>	1607				3218		61BCJ146

<sup>a</sup> Numbering according to formulas **295**, **301**, and **297**, respectively. <sup>b</sup> Stretching frequencies in cm<sup>-1</sup> [in KBr or (**85**, **188**) CHCl<sub>3</sub>]. <sup>c</sup> Broad OH and NH band.

isomers **292** and **293** (23 and 15  $\text{cm}^{-1}$ , respectively) and furothienotropones **313** and **314** (48  $\text{cm}^{-1}$ ). This effect is absent in  $[c,c']$ -fused compound **312** and in dibenzotropone.

In tri- and tetracyclic indolotropones, the  $\text{C}=\text{O}$  stretching bands also exhibit much lower values than those in the corresponding tetrahydro and dihydro derivatives [70JPR(312)466; 72BCJ269]. In the case of cycloheptapyrazin-5-ones, however, dehydrogenation in the heterocyclic ring causes the  $\text{C}=\text{O}$  band to shift from 1600 up to 1655  $\text{cm}^{-1}$  by loss of hydrogen bonding with the NH proton [83H(20)1117].

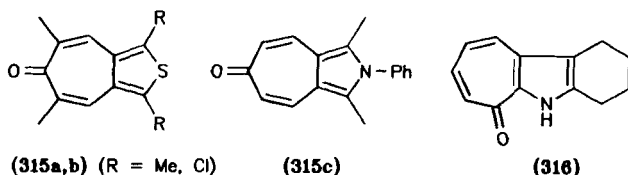
In thieno[*c*]tropones **315a,b** (Scheme 79) the  $\text{C}=\text{O}$  bands are observed at 1572 and 1610  $\text{cm}^{-1}$ , respectively (67JOC1610). The higher value of **315b** shows that the chlorine atoms hinder delocalization of electrons from sulfur to oxygen. In similar thieno- and pyrrolotropones, the introduction of a methyl group into the 5- or 7-positions causes a small fall (about 10  $\text{cm}^{-1}$ ) in the  $\text{C}=\text{O}$  frequency (69ZOR570).

In pyrimidotropones **94b-d** and their homologs, the amino substituents at C-2 influence the  $\text{C}=\text{O}$  band position (92JHC795). The bands shift in the range  $\text{NMe}_2$  (**94d**) <  $\text{NHMe}$  (**94c**) <  $\text{NH}_2$  (**94b**) from 1585–1581 to 1587–1583 and 1607–1605  $\text{cm}^{-1}$ .

In 5,7-polymethylene derivatives of cyclohepta[*c*]furan-6-ones, the  $\text{C}=\text{O}$  band is shifted from 1682 down to 1628  $\text{cm}^{-1}$  on lengthening the ansa chain from 7 up to 10 members (85MI3).

Guilard and co-workers (75MI1), who studied solvent effects on the  $\text{C}=\text{O}$  bands of thienotropones, observed expected shifts directed to lower wave numbers in more polar solvents. The same dependence is found in furo[*c*]tropone **307a** (68T4501), the position of which in the  $\text{C}=\text{O}$  band range (above benzotropone and tropone) corresponds to the higher bond order as calculated by the HMO method (68TL3771; cf. Section III,A,3).

The  $\text{C}=\text{C}$  stretching bands of the fused tropone ring are reported to lie in the region between 1640 and 1595  $\text{cm}^{-1}$  [e.g., 82CZ411; 84H(22)791; 91GEP4037187]. Often two  $\text{C}=\text{C}$  bands are observed (cf. Table XVII and 73CRB293, p. 326). The corresponding olefinic  $\text{CH}$  bands are found between 3100 and 3000  $\text{cm}^{-1}$  (e.g., 72BCJ269; 91CB2465) and sometimes at lower values (82CZ411).



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Furthermore, Guillard and co-workers [75MI1; 80BSF(1)327] analyzed the IR spectra of ten thienotropones and -tropolones (among others, compounds **306b–310b**) and corresponding deuterated derivatives over the range 4000–200  $\text{cm}^{-1}$ . They tabulated complete assignments of CH and CD stretching and deformation vibrations of tropone and thiophene rings, together with 23 fundamental vibrations.

The same group [71CR(273)160] proved that C=O and C=C stretching bands of thieno[*c*]troponoids are found at wave numbers higher than those of the thieno[*b*]-fused isomers. The presence of methyl groups is usually expressed by lower wave numbers.

Sato (63CPB1431, 63CPB1440) assigned bands (840–825  $\text{cm}^{-1}$ ) in the fingerprint region of pyrrolotropolones (e.g., **179b**, **366**, **368**, **369**, **548**; Schemes 43, 98, and 145) to the out-of-plane deformation vibrations of two adjacent hydrogen atoms of the tropolone rings (cf. 59MI1, p. 375).

Because of intramolecular hydrogen bonding, the *OH stretching frequencies* of fused tropolones are distinctly lowered (as in tropolene itself) and lie at wave numbers between about 3350 and 3150  $\text{cm}^{-1}$  [63BCJ173; 65BCJ362; 71CR(273)160; 75MI1]. The C=O frequencies are lowered as well.

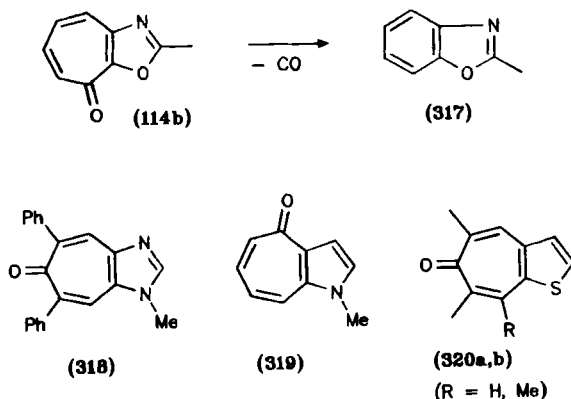
In troponoids with fused nitrogen heterocycles *NH stretching bands* are observed in the region between 3420 and 3080  $\text{cm}^{-1}$  [69MI1; 76BCJ1101; 89BCJ128; 90H(31)677; 93T113]. As in the case of tropone C=O bands, dehydrogenation of a partially saturated seven-membered ring lowers the NH frequency of the fused pyrrole moiety. However, dehydrogenation of the six-membered ring in fused tropones, for example, **316**, increases the position of the NH vibration (75BCJ314).

e. *Mass Spectrometry.* In monocyclic tropones and tropolones (73CRV293, p. 328), besides the molecular ion peak, the most prominent peak or even the base peak corresponds to loss of CO ( $M^+ - 28$ ). Fused troponoids behave similarly.

Mass spectra of heterocyclic troponoids have been reported since 1965. Again, in most cases the molecular ion or the  $(M - \text{CO})^+$  ion forms the base peak; this is seen, for instance, in pyridotropones **13a–c** [77TL2663; 90JCS(P1)435], pentacyclic furotropone **53a** (92T5481), and pyrrolotropone **646** [see Scheme 173; 94JCS(P1)2579].

Jin (92MI4) found the decarbonylation of the tropone rings of azolotropones (e.g., **85**, **86a**, **87a**, **90**, **91**, and **114b**) to be the first step of the fragmentation. The heterocyclo-fused benzenoid compounds thus formed are further fragmented in the same manner as the original benzo derivatives. In this way, oxazolotropone **114b** (Scheme 80) decarbonylates into benzoxazole **317**, which further expels CO and  $\text{CH}_3\text{CN}$  (74UP1).

The fragmentation can also start in the heterocyclic moiety of these compounds. Thus, imidazole **318** loses HCN or  $\text{CHNMe}$  (820PP409); imid-



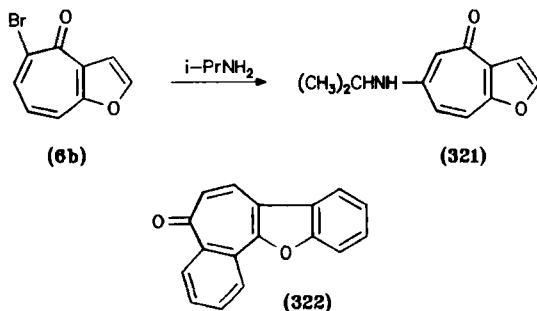
SCHEME 80

azoles **186a** and **b** lose Ac or CPh, respectively, from the side chains (92JHC1219); and *S*-oxides (e.g., **68**) or *N*-oxides (e.g., **326**) first yield the desoxygenation fragments  $M^+ - 16$  [84H(22)467 and 74JOC2956, respectively].

In a unique pathway, cyclohepta[*b*]furan-6-ones such as **404a** (Scheme 95) first lose CO from the tropone *or* from the furan rings (94RRC41).

In cases of parallel fragmentation of both tropone and heterocyclic rings, pyrrolo[2,3-*b*]tropone **319** loses CO and NMe [80JCS(P1)2081], whereas imidazotropones **185b** expels CO and Et (92JHC1219); 2-phenylpyrazolotropone first loses CO, then Ph [93JCS(P1)1617]. Thienotropones **320** were thoroughly studied [80PS(9)165]; compound **320b** successively expels CO, H, Me, etc. (from the tropone ring) and HCS, etc. (from thiophene).

The mass spectrum of furotropone **321** (Scheme 81; formation in Section IV,A,4,e) is characterized by the attack on the side chain of the tropone ring [80JCS(P1)2081]; consequently, Me, *i*-Pr, and *i*-PrN are lost.



SCHEME 81

Among tricyclic compounds, ditropolonofuran (utahin) **162** successively loses two CO fragments and Me [68JCS(CC)233]. Tetracyclic dibenzofurotropone **322** and its derivatives expel CO (followed by CHO) or C<sub>2</sub>H<sub>2</sub> [78IJC(B)567], and similar benzindolotropolone **324** (see Scheme 83) loses two CO fragments in two steps (78BCJ3579).

The mass spectrum of tricarbonyliron cyclobutadiene derivative **282** shows fragments corresponding to the stepwise loss of four CO molecules and finally of C<sub>2</sub>H<sub>2</sub> (78AJC1607).

Furthermore, mass spectrometry served for the structural elucidation of such natural products as thiotropocin **168**, derivatives of the latter compound (84TL419), and the isomeric dimethyl ethers **418a–c** of anhydrosepedonin **169** (69MI3; 72CJC821).

f. *Other Spectroscopic Methods.* The Raman spectra of ten thienotropones and -tropolones (compounds **306b–310b** and homologs) were analyzed (75MI1). The photoelectron spectra of seven [c]-fused furo-, thieno-, and pyrrolotropones (among others, **264a,b**, **307a,b**, **320b**) were investigated and the peaks were assigned using quantum chemical calculations (84BCJ856).

### 3. Aromaticity, Planarity, Polarity, and Stability

Early studies on resonance stabilization of troponoids seemed to prove great contributions of aromatic tropylium oxide structures [55CRV9, p. 118; 56AG661; 56FOR(13)232, p. 262; 56MI2, p. 318; 59MI1, p. 374].

Later, it was found that the significance of high dipole moments, low IR carbonyl frequencies, and other results had been overestimated. Tropone exhibits double-bond alternation and thus is more properly regarded as an unsaturated ketone without *much* contribution of charge separation. In tropolone, however, the carbon-carbon bonds only slightly alternate, and hence are very similar to typical aromatic bonds (66MI2, p. 129; 73CRV293, p. 325; 74MI1; 84MI2, pp. 91 and 109; 90MI3, p. 111).

In benzo- and dibenzotropones, whose seven-membered rings deviate from planarity, bond alternation was proved (73CRV293, p. 328).

In the series of heterocyclic fused analogs, Cook *et al.* (68T4501, 68TL3771) compared the properties of cyclohepta[c]furan-6-one (**307a**) with those of benzo[d]tropone and tropone by means of HMO calculations, spectra, and chemical reactivity (carbonyl derivatization). Whereas the two fused systems are comparable, their aromatic character is still less than that of tropone.

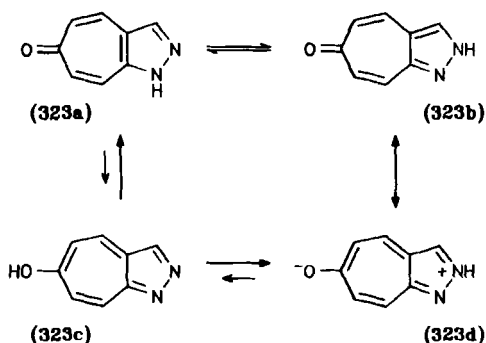
Furthermore, Trinajstić and co-workers [68MI1; 71ZN(B)1007] reported the results of calculations (HMO, SCF) that support bond-alternating structures for the seven possible furotropones. Each shows less delocalization energy and less "aromatic stabilization" ( $A_s$ ) than benzo[*b*]- and benzo[*d*]tropone.

Among tricyclic systems, spectroscopic and X-ray crystallographic results suggest that thieno- and selenophenotropones **234b** and **c** are planar [83CS(22)53]; however, ditropolonofuran **162** [76AX(B)3118; cf. Section III,A,1] and a similar ditroponofuran (67TL433) seem to lack full planarity. In some cases, bond-length alternation was proved.

The comparison of isomeric isoxazolotropones **90** and **91** (82JHC525) indicates that the latter is less aromatic: The UV maxima are shifted bathochromically (Table XIV) and the broad  $^1\text{H-NMR}$  peak for the tropone ring protons is found at higher field than the peak of isomer **90**.

Jones *et al.* [73JCS(P1)968] assume that delocalization over the whole fused system of furo- (**6a**), pyrido- (**304**), and thienotropones is minimal because the  $^1\text{H-NMR}$  data of their tropone rings are similar even though the electron availability in the heterocyclic rings is very different. However, Jin (92MI2) found differences in the contribution of  $10-\pi$  systems of several azolotropones (cf. Section III,A,2,c).

With respect to parent pyrazolotropone **323**, the following order of aromaticity can be given (72JOC676): tropone > benzo[*d*]tropone > **323** > furo[*c*]tropone **307a**. A significant contribution of the dipolar structure **323d** is postulated (Scheme 82). Similar mesomeric zwitterionic forms are proposed for tropone-fused nitrogen or sulfur heterocycles such as pentacyclic pyrrolotropone **53b** (64JCS5096), benzoxazinotropone **267** (83BCJ2756), and thienotropone **315a** (67JOC1610). It is stressed, however, that the intramolecular polarization in **315a** does not lead to the full separa-



SCHEME 82

tion of charges (67ZOR191), although the presence of alkyl substituents in tropones tends to increase polarization (69ZOR570).

The dipole moments of some fused tropones and tropolones are listed in Table XVIII.

Eventually, such heterocyclic systems as furan and indole are found to be stabilized by fusion to tropolone systems, as in the cases of compounds **11a** (54CB1197) and **301** [57LA(608)38].

Kurihara *et al.* (90BCJ2531) discussed the stability and resonance energy of troponoids by application of the "topological charge stabilization" (TCS) rule. Many synthetic and natural troponoids prove to be energetically very stable molecules. The TSC rule can be applied to the formation mechanism of heterocyclotropones. Many benzazinetropone products are completely consistent with this rule, for example, tri- and higher-cyclic quinoxalotropones **27** and **166**.

#### 4. Tautomerism and Other Isomerisms

a. *Prototropic Tautomerism.* Monocyclic tropolone appears in solution in two forms, each bearing the acid proton at one of the oxygen atoms; both forms contribute equally to the tautomeric equilibrium (76MI1, p. 208; 84MI2, p. 109; 90MI3, p. 116). The  $^{13}\text{C}$ -NMR spectrum consists of just four singlets, suggesting rapid equilibration even at low temperature. Because of this tautomerism, separated isomers of unsymmetrically carbon-substituted tropolones cannot be isolated.

TABLE XVIII  
DIPOLE MOMENTS OF CYCLOHEPTATHIOPHEN-6-ONES AND -PYRROL-6-ONE

Fused heterocycle	Further substituents	Formula no.	Dipole moment (D)	Reference
[b]thiophene	—	<b>306b</b>	4.85	70CR(C)1905
	5-Me	—	4.34	
	5,7-di-Me	<b>320a</b>	3.79	
	5-OH	<b>308b</b>	4.06	
	5-OMe	<b>36</b>	4.98	
[c]thiophene	—	<b>307b</b>	4.52	
	5-Me	—	3.95	
	5,7-di-Me	<b>465b</b>	3.46	
	5-OH	<b>310b</b>	3.80	
	5-OMe	—	4.50	
[c]pyrrole	2-Bu-1,3-di-Me	<b>264c<sup>a</sup></b>	8.3	79CB2087

<sup>a</sup> Corresponding troprothione (**557**): 9.1 D.



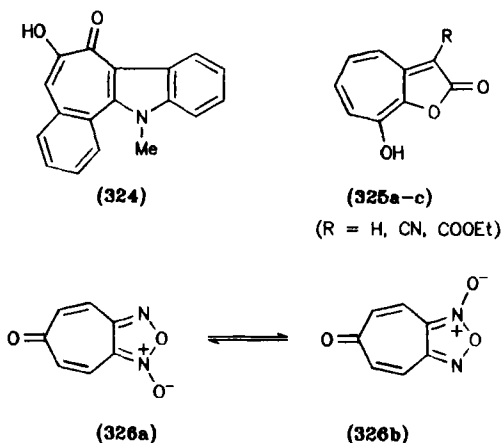
In principle, a similar tautomerism is possible in fused tropolones. Thus, *O*-methylation can lead either to one tropolone methyl ether (62BCJ808) or to two isomers, as in the case of anhydrosepedonin derivatives **418b** and **c** (Scheme 112; 69MI3). The yield of isomer **418c** is very low, as expected.

Furthermore, some fused tropolones give typical reactions of *o*-dihydroxy or *o*-diketo (**389**) tautomers; they form *o*-dimethoxy compounds (e.g., **418a**) or derivatives of dicarbonyl compounds (dioximes and quinoxalines like **513**), respectively (65MI3). Another diketone exhibits remarkable stability against enolization to form indolotropolone **324** (Scheme 83), due to steric interaction (78BCJ3579).

Azaazulenones and benzazinetropolones without *N*-substitution also show tautomerism. The keto forms (such as **323a,b** and **406**; Schemes 82 and 108) predominate over the hydroxy tautomers like **323c** [72JCS(P1)1623, 72JOC676; 79BCJ1972]. In the case of pyrrolo[*b*]tropolones (54MI2; 77BCJ1184), imidazotropolones (54MI3; 62BCJ1188), triazotropolones (54MI1), benzoxazinetropolones (e.g., **22**, **267**, **297**; 83BCJ2756; 91BCJ2131), and benzothiazinetropolones (e.g., **123**; 61BCJ146; 66BCJ1980), the results were established by spectroscopic studies and by theoretical calculations.

In imidazotropolone **105a**, the keto structure is supported by its spectral similarity to nontautomeric *N*-benzylated derivatives (69MI1). Even in pyrrolotropolone **181**, whose carbonyl group is in a  $\beta$  position relative to the bridgehead, the keto form is supposed to dominate (65BCJ306).

Enolic structures were established in lactonic compounds **325a-c** (64BCJ1460; 71T6023); they are monobasic acids (**325c**:  $pK_a$  3.57). In an early paper (58MI1) the lactim form of pyrazolotropolone **388** was taken into account. In the case of diazepinetropolone **95** (79MI3), the lactim form was preferred (81JHC335).



SCHEME 83

Investigations on the tautomerism of fused heterocyclic moieties favor the lactam form of the imidazole substructure of **16** (65CPB473) and the thiolactam tautomer in thiazoles **192** and **197** [62BCJ1998; 64BCJ1526; 95PS(101)167], but the hydroxy form in pyrazole **183** [82IJC(B)765].

b. *Valence Tautomerism.* The diene reaction of troponooxepine **156a** gives the cycloaddition product of troponobenzene oxide (88CL1647); hence, valence tautomerism is assumed.

c. *Other Isomerisms.* Rotational isomerism was revealed by NMR studies of pyrrolotropones **299a,b** (Section III,A,2,a; 80BCJ3373).

For the isomerization of furoxan **326a** and **b**, a lower limit of 24 kcal mol<sup>-1</sup> was estimated for the free energy of activation for the rearrangement (74JOC2956).

## 5. Polarographic Reduction

Early studies of monocyclic troponoids (55CRV9, p. 116) in acidic and in basic solutions showed a single reduction step or two reduction steps, respectively. Later, similar results were obtained, especially by Etaiw *et al.*, in detailed studies of furo- and thienotropones [69ZOB46; 71CR(273)160; 80CJC263, 80CJC2358] and -tropolones [82AC(R)191]. The carbonyl group was found to be the sole active center for reduction.

Thus, at low pH values, the reduction of tropones proceeds via one-electron waves to form free radicals that dimerize to produce pinacols. At mean pH values, two waves are found, each corresponding to 1 F. In strong alkaline media, one wave is observed that, in many cases, corresponds to the uptake of two electrons, proceeding via the anion-radicals to form tropols.

In the case of tropolones **308–310** (Scheme 77), the one- and two-electron waves reflect pH values lying, respectively, below or above the p*K* values of the corresponding substances. (Electron affinities, ionization potentials, and polarographic oxidation potentials were also determined.) Indolotropolone **301** shows a similar pH dependence [57LA(608)38].

## B. TROPYLIUM SALTS

### 1. X-Ray Diffraction

The molecular geometries of dithienotropylium ions **237b** and **238b** (Scheme 57) have been studied by X-ray diffraction. Cation **237b** [79AX(B)1349], which is nearly planar, is slightly less bent and slightly

more aromatic than the corresponding tropone **291** (Scheme 73). This tropone is approximately mirror-symmetric with the two nonplanar thiophene rings (A and B); in cation **237b** only ring A is nonplanar.

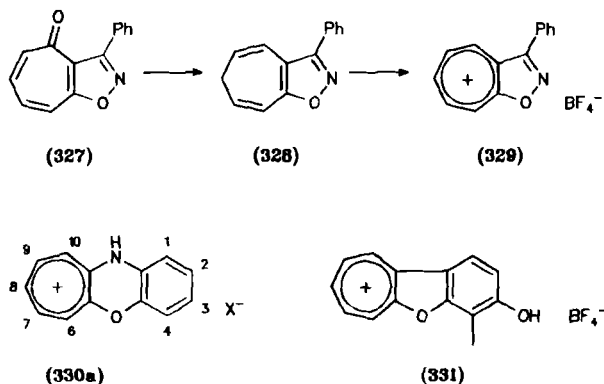
Tropylium ion **238b** [74ACS(B)681; 81AX(B)401] is approximately planar, symmetric, and even more aromatic than **237b**. It exists in two phases (I and II), with small and large unit cells, respectively (examined at 295 K and 173 K, respectively). Phase II seems to be metastable at higher temperatures.

## 2. Molecular Spectra

a. *<sup>1</sup>H-NMR Spectra.* The parent tropylium ion shows a single, sharp signal at extremely low field, about  $\delta$  9.3 (73CRV293, p. 335; 73MI2, p. 1596). Table XIX presents some bicyclic derivatives and their typical NMR data extending up to the same  $\delta$  region.

The comparisons in Tables IX and XIX (e.g., of compounds **51** and **221**) reveal the strong low-field shifts (especially of the seven-membered-ring protons) of about 2 ppm that accompany the transition from troponoids to tropylium compounds. In the synthetic sequence from tropones via tropylienes to tropylium salts (e.g., from **327** to **329**, Scheme 84), even larger low-field shifts are noted between the methine protons of (less aromatic) tropylienes like **328** and those of tropylium salts (74T3765; 86CL1925).

The spectra of furotropolones (e.g., **307a**) were compared in CF<sub>3</sub>COOD solution (which contains salt **336a**) and in CDCl<sub>3</sub> solution. In the acidic medium, downfield shifts (0.7–1.3 ppm) of the seven-membered-ring protons and decreased (0.5–1.2 Hz)  $J_{45}$  values were observed (94TL8421).



SCHEME 84

TABLE XIX  
<sup>1</sup>H-NMR CHEMICAL SHIFTS OF TROPYLIUM SALTS WITH FUSED FIVE-MEMBERED HETEROCYCLIC RINGS (Type **333**)<sup>a</sup>

Fused heterocycle <sup>b</sup>	Substitution	Formula no.	$\delta$ (ppm) <sup>c</sup> in positions								Solvent <sup>d</sup>	Reference
			1	2	3	4	5	6	7	8		
[b]furan	5,7-di-Me <sup>e</sup>	—	—	8.68	7.50	9.02	(3.15)	8.82	(3.15)	9.27	TFA	77BSF(2)75
[c]furan	5,6,7-tri-Me	—	7.86	—	7.86	9.04	……	(3.15)	……	9.04		85MI1
[b]thiophene	—	<b>221</b>	—	9.13	8.48	9.68	……	8.85	……	9.68	DS	71BSF1437
[c]thiophene	1,3-di-Me	—	(3.17)	—	(3.17)	9.00	7.86	8.57	7.86	9.00	TFA	69ZOR570
	5,7-di-Me	<b>491</b>	9.30	—	9.30	9.35	(3.35)	8.90	(3.35)	9.35	TFA	74YZ1429
	6-OH	—	8.90	—	8.90	8.78	7.60	—	7.60	8.78	TFA	
	1,3-di-Me-6-OH	—	(2.88)	—	(2.88)	8.44	7.20	—	7.20	8.44	TFA	69ZOR961
[c]pyrrole	2-Ph-1,3,5,7-tetra-Me	<b>228b</b>	(2.62)	—	(2.62)	8.70	(2.72)	8.22	(2.72)	8.70	TFA	68ZOR907
	1,3-di-Me-6-OH-2-Ph	—	(2.57)	—	(2.57)	8.49	7.10	—	7.10	8.49	TFA	69ZOR961
	1,3-di-Me-6-SMe-2-Ph	<b>605</b>	(2.61)	—	(2.61)	8.69	7.52	(2.93)	7.52	8.69	CDCl <sub>3</sub>	91KGS1432

<sup>a</sup> Perchlorates except **605** (iodide). <sup>b</sup> [b]- and [c]-fusion as given in formulas **333** and **338**, respectively. <sup>c</sup> See Table X, Footnote (b). <sup>d</sup> TFA = CF<sub>3</sub>COOH, DS = deuterated solvent. <sup>e</sup> Similar shifts are found in the tetracyclic analog **246** (92KGS1142).

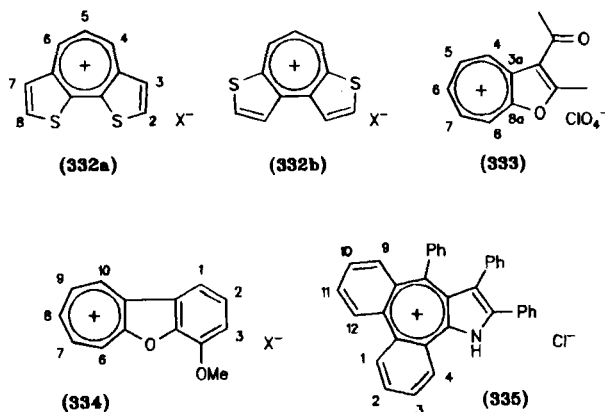
Moderate low-field shifts of about 0.5–1.3 ppm are also observed in the case of benzotropazines, for example, between tropone **267** (Table XI) and tropylium salt **330a** (78CBJ2185, 78BCJ3316; 79BCJ3123; 88BCJ271; 89BCJ1158). However,  $\delta$  values up to 9.8 were found for seven-membered-ring protons of azolo- (**23b,c**) and benzofurotropylium compounds (**331**) [67CPB619; 71JCS(C)2399].

Large shifts of up to  $\delta$  9.92 ppm were also found in the case of bis-fused tropylium salts **332a,b** (Scheme 85; 78T587) and some isomeric ions (e.g., **351**, Scheme 92; 78JHC285). These shifts culminate in  $\delta$  values up to 10.30 ppm for systems like **236–238** [70ZC389; 73ACS2257; 83CS(22)53] and **263** (75TL1849). In the seven-membered rings, the largest  $\delta$  values were found for the formal methine protons in positions 4 (**237**), 9 (**238**), 10 (**236**), or 11 (**263**). This fact is due to the partial localization of the positive charge onto the respective carbon atoms (Section III,B,3,a).

As in the case of troponoids (Section III,A,2,a; Table XII), additional low-field shifts of certain tropylium-ring protons were attributed to deshielding neighboring groups: for instance, the acetyl group in **333** (H-4:  $\delta$  10.20 ppm; 77BCJ3425) or the furan oxygen atom in **334** (H-6:  $\delta$  9.79 ppm; 67BCJ1480).

Similarly, in the tricarbonyliron cyclobutadiene complex **285** (78AJC1607), the metal carbonyl groups stabilize the positive charge in the  $\alpha$ -positions to the complexed diene system (H-2 and H-6:  $\delta$  8.29 ppm).

However, complexation of dibenzotropylium ion **290a** [83AG572, 83AG(S)734] or thienotropylium ion **352b** [Scheme 157; 71JOM(33)195] to  $\text{Cr}(\text{CO})_3$ , forming **290b** and **588**, respectively, causes high-field shifts of the proton signals.



SCHEME 85

Introduction of a phenyl group into the 6-position of thieno- or pyrrolo[c]-tropylium ions (e.g., transition from **228** to **230**) shifts the 5- and 7-methyl protons to high field (0.4 ppm); consequently, noncoplanarity of the 6-phenyl ring and heterocyclotropylium system must be concluded (68-ZOR907).

b. <sup>13</sup>C-NMR Spectra. The monocyclic tropylium ion shows a singlet at 160.6 ppm (73CRV293, p. 335). In Table XX, assignments of signals for some heterocyclic fused compounds are listed. Most of the signals appear at lower field than those of the respective tropone derivatives (compare Tables XX and XIII, e.g., substances **266c** and **264c**), but they are found at much lower field than the corresponding resonances of the tropylidene derivatives (compare **218** and **217**; 80TL3375).

The <sup>13</sup>C-chemical shifts of tropylium salts **218**, **329**, and **333** (Table XX) were plotted against the electron densities calculated by the HMO method. Most points fall on straight lines, except those for oxygen-bonded carbons (C-2, C-8a), which exhibit more deshielding than expected from the calculated electron densities.

c. Electronic Spectra. After earlier findings (56AG661; 68MI2) were revised, the parent tropylium ion was found to absorb only in the UV region (73CRV293, p. 336; 73MI2, p. 1593). In Table XXI, the tropylium spectrum (first entry) is compared with the spectra of fused analogs that generally absorb at higher wavelengths; mostly, they are colored.

Although tropylium salts usually show *bathochromic shifts* with respect to the corresponding troponoids (compare Table XXI with Tables XIV and XVI, e.g., substances **221** and **51**), they show even higher shifts with respect to the precursor tropylidenes (e.g., from 320 up to 634 nm for furan **333**; Table XXI).

However, tricyclic pyrrolotropylium ion **647** [Scheme 173; 94JCS(P1)2579] absorbs at a shorter wavelength than the corresponding hydrocarbon, the cycloheptazulenium ion, but with similar fine structure.

High values of the longest wavelength absorptions were also found for tricyclic compounds such as **238b** (up to 470 nm: 70ZC389; 73ACS2485) and for the nearly black tetracyclic pyrrole **335** (540 nm: 72CB1224), the deep violet iron complexes **285** and **288** (up to 550 nm: 78AJC1607 and 70JA6382, respectively), the chromium complex **290b** [628 nm: 83-AG(S)734], and, especially, for such quinoxalines as **224c** (up to 752 nm: Table XXI).

For a number of [c]-fused 1,3,5,7-tetramethyl derivatives having azulene-type electronic spectra, the  $\lambda_{\max}$  values of the longwave maxima increase from 540 to 706 nm in the following series (El'tsov and co-workers; Table

TABLE XX  
<sup>13</sup>C-NMR CHEMICAL SHIFTS OF TROPYLIUM SALTS WITH FUSED FIVE-MEMBERED HETEROCYCLIC RINGS (TYPE 333)

Fused heterocycle <sup>a</sup>	Substitution or further fusion	Anion	Formula no.	$\delta$ (ppm) in positions										Solvent	Reference
				1	2	3	3a	4	5	6	7	8	8a		
[b]furan	—	BF <sub>4</sub> <sup>-</sup>	218	—	160.1	115.5	150.9	150.5	137.0	146.3	143.8	145.1	166.1		80TL3375
	3-Ac-2-Me	ClO <sub>4</sub> <sup>-</sup>	333	—	176.9	122.6	149.8	145.9	147.2	151.0	145.4	136.9	165.2	CD <sub>3</sub> CN	77BCJ3425
	2,3-benzo <sup>b</sup>	ClO <sub>4</sub> <sup>-</sup>	248	—			161.1	150.5	(147.2/144.5/138.5)			148.0	169.8	CD <sub>3</sub> CN	81AJC1037
[c]furan	6-OH	CF <sub>3</sub> COO <sup>-</sup>	336a	151.4	—	151.4	126.8	147.9	126.6	193.7	126.6	149.7	126.8	CF <sub>3</sub> COOD	94TL8421
[c]pyrrole	2-Bu-1,3-di-Me-6-Cl	ClO <sub>4</sub> <sup>-</sup>	(266c)	140.3	—	140.3	128.7	129.8	147.0	162.8	147.0	129.8	128.7	CD <sub>3</sub> NO <sub>2</sub>	79CB2087
	2-Bu-1,3-di-Me-6-SMe	I <sup>-</sup>	559	135.9	—	135.9	125.0	123.8	142.6	177.8	142.6	123.8	125.0	CDCl <sub>3</sub>	
[d]isoxazole	3-Ph	BF <sub>4</sub> <sup>-</sup>	329	—	—	164.0	140.2	156.3	136.4	152.1	147.7	149.3	175.1	CD <sub>3</sub> CN	86CL1925

<sup>a</sup> [b]-, [c]-, and [d]-fusion as given in formulas 333, 338, and 329, respectively. <sup>b</sup> For convenience, the numbering is that of the bicyclic system (333); assignments at C-5,6,7 are tentative.

TABLE XXI  
UV-VIS MAXIMA OF TROPYLIUM SALTS WITH FUSED HETEROCYCLIC SYSTEMS (TYPES **333** AND **330a**)

Fused system <sup>a</sup>	Substitution	Anion	Formula no.	Color (crystals)	$\lambda_{\max}$ in nm (log $\epsilon$ )					Solvent	Reference
— <sup>b</sup>	—	ClO <sub>4</sub> <sup>-</sup>	<b>220</b>	—	217 (4.61)	273 (3.63)				96% H <sub>2</sub> SO <sub>4</sub>	73CRV293, p. 336
benzene	—	ClO <sub>4</sub> <sup>-</sup>	<b>350a</b>	yellow	234 (3.25)	282 (3.54)	338 (4.74)			60% H <sub>2</sub> SO <sub>4</sub>	57HCA957
					426 (4.30)						
[b]furan	—	BF <sub>4</sub> <sup>-</sup>	<b>218</b>		254 (4.68)	295 (3.44)	359 (3.79)			96% H <sub>2</sub> SO <sub>4</sub>	80TL3375
	3-Ac-2-Me	ClO <sub>4</sub> <sup>-</sup>	<b>333</b>	greenish-blue	218 (4.39)	260 (4.43)	363 (3.85)			MeCN	77BCJ3425
					634 (2.46)						
[b]thiophene	—	ClO <sub>4</sub> <sup>-</sup>	<b>221</b>	yellow	284 (4.7)	323 (3.6)	340 (3.5)			water	63TL401
					408 (3.3)						
[c]thiophene	1,3,5,7-tetra-Me-6-OH <sup>c</sup>	ClO <sub>4</sub> <sup>-</sup>	<b>239</b>	dark-red	264 (4.16)	310 (4.70)	360 (4.07)			42% HClO <sub>4</sub>	67ZOR191
					372 (4.02)	540 (3.35)					
	1,3,5,7-tetra-Me-6-OMe	BF <sub>4</sub> <sup>-</sup>	<b>240</b>		274 (4.16)	325 (4.54)	373 (3.92)			ethylene chloride	69ZOR961
					390 (4.03)	600 (3.25)					
	1,3,5,7-tetra-Me	ClO <sub>4</sub> <sup>-</sup>	<b>228a</b>	dark-blue	242 (4.16)	280 (4.40)	322 (4.24)			42% HClO <sub>4</sub>	67ZOR191
					375 (3.43)	680 (3.31)					
[c]pyrrole	2-Ph-1,3,5,7-tetra-Me	ClO <sub>4</sub> <sup>-</sup>	<b>228b</b>		279 (4.50)	363 (3.89)	706 (3.25)			5% HClO <sub>4</sub> /AcOH	68ZOR907
[d]isoxazole	3-Ph	BF <sub>4</sub> <sup>-</sup>	<b>329</b>		235 (4.37)	280 (3.85)	353 (2.81)			MeCN	86CL1925
quinoxaline	—	BF <sub>4</sub> <sup>-</sup>	<b>344</b>	dark-green	236 (4.16)	289 (4.46)	331 (3.89)			MeOH	89BCJ1158
					445 (3.84)	464 (4.00)	564 (3.01)				
					616 (2.91)	670 (2.83)	752 (2.34)				
	5,11-di-Me	Cl <sup>-</sup>	<b>224c</b>	dark-green	238 (4.18)	287 (4.23)	328 (3.84)			MeOH	
					440 (3.81)	578 (3.07)	620 (3.05)				
					732 (2.56)						
benzoxazine	11-Me	BF <sub>4</sub> <sup>-</sup>	<b>224a</b>	dark-red	228 (4.31)	264 (4.22)	272 (4.31)			MeOH/HBF <sub>4</sub>	85BCJ165
					320 (3.78)	428 (3.83)					
benzothiazine	11-Me	BF <sub>4</sub> <sup>-</sup>	<b>224b</b>	dark-red	240 (4.39)	282 (4.26)	340 (4.04)			MeOH	
					452 (3.68)						

<sup>a</sup> See Table XX, Footnote (a). <sup>b</sup> Parent tropylium ion. <sup>c</sup> Corrected structure (69ZOR961).



XXI): thieno (6-OH) (**239**) < thieno (6-OMe) (**240**) < thieno (6-H) (**228a**) < pyrrolo (6-H-2-Ph) (**228b**).

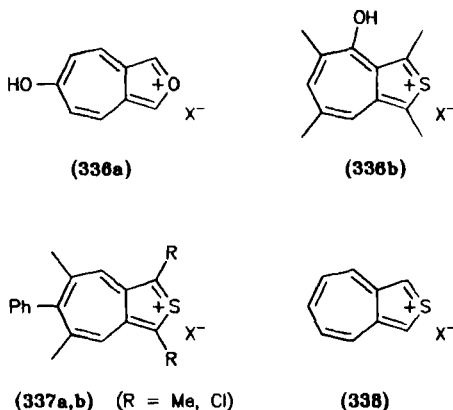
Among 6-alkyl and 6-aryl derivatives of salts **228a,b**, the location of the maximum ( $\lambda_{\max} = 652\text{--}720\text{ nm}$ ) exhibits little dependence on the nature of the heteroatom (2-position) or the substituent at C-6 (68ZOR907; 69ZOR961), but rather is determined by the azulene moiety—i.e., by the electronic contribution of heteronium structures like **341b** (see Scheme 88).

In analogy to Plattner's rule from azulene chemistry (84MI2, p. 361), introduction of a methyl group onto C-6 of these alkyl and aryl derivatives (e.g., **228**) shifts the longwave band hypsochromically (by 20–30 nm), whereas a methyl group at C-5 shifts the band bathochromically by 10–20 nm (68ZOR907; 69ZOR570). A phenyl group at the 6-position does not affect this band (e.g., in **230**) unless the 5- and 7-positions are unsubstituted; in this case, a new band at about 400 nm appears (the band of sterically unhindered phenyl conjugated with the tropylium ion).

In derivatives of the 6-hydroxyfuro[c]tropylium ion **336a** (Scheme 86), the longest wavelength band shifts bathochromically by about 40 nm on introduction of a methyl group at C-1 and C-3; the spectra are similar to those of 6-hydroxyazulene derivatives (94TL8421).

Furthermore, a comparison of the 4- (**336b**) and the 6-hydroxy derivative (**239**) of thiophene **228a** shows their longwave bands lying at 585 and 540 nm, respectively (70ZOB2078). The larger value for the unsymmetrical **336b** is due to lower conjugation between the hydroxy group and the cationic moiety.

Guilard *et al.* [71CR(273)160] observed a characteristic tropylium band between 260 and 300 nm ( $\log \epsilon$  3.64–4.89) and found the follow-



SCHEME 86

ing range of increasing wavelengths among parent tropylium (**220**), 5,7-dimethylfuro[*b*]tropylium, 6,8-dimethylbenzotropylium (**350b**, Scheme 92), and seven-membered-ring substituted thieno[*b*]- and -[*c*]tropylium derivatives: furo[*b*] (259 nm) < **220** (274 nm) < **350b** (282 nm) < thieno[*b*] (282–290 nm) < thieno[*c*] (299–303 nm).

The bathochromic effect of methyl groups is small (about 2 nm). An additional band in the region 305–345 nm ( $\log \epsilon$  3.48–3.76) was found in the spectra of the [*b*]-series and the benzo derivative. Only the thieno[*b*]tropylium salts exhibit a third band at 338–346 nm ( $\log \epsilon$  3.57–3.78). Dichlorodimethyl compound **337b**, compared with the tetramethyl derivative **337a**, shows a bathochromic shift of about 10 nm (67JOC1610).

Since the UV spectra of certain tropylium salts are pH-dependent, they are best taken at a low pH value (56AG661; 85BCJ165). Isoxazole **329** provides an example of solvent dependence: The spectrum taken in ethanol is quite different from that taken in acetonitrile (86CL1925).

*Quantum-chemical calculations* of a variety of sulfur-containing heterocycles have been used to interpret (among other things) the electronic spectra. Thus, the properties of thienotropylium ions **221** and **338** have been calculated both by HMO (65CCC3016) and by PPP procedures (68JPC3975). Moreover, the calculated (PPP) spectra of tricyclic cations **237** and **238** were found to be in good agreement with the experimental spectra (73ACS2485).

Pentacyclic bis(quinoxalotropone) **166** (88CL175), which is planar and symmetrical, exhibits remarkable spectral properties:

1. distinct solvatochromism in organic solvents;
2. time-dependent electronic spectra in trifluoroacetic acid;
3. time-dependent  $^1\text{H}$ -NMR spectra in the same solvent, the signals becoming broadened and moving to higher field;
4. narrow and strong bands in the absorption and fluorescence spectra taken in concentrated sulfuric acid solution;
5. broad ESR signals in the same solvent.

Presumably, the dication obtained in sulfuric acid is a fully conjugated aromatic peripheral 22- $\pi$  system that forms *J*-aggregates—previously observed exclusively in cyanine dyes. Only a few related compounds were found to give the same effect; the structural requirement for *J*-aggregation in these systems has been described (89CL1719). The optical properties of the corresponding propyl derivatives assembled in monolayers were studied (94MI4).

d. *Infrared Spectra.* Because of the high symmetry of the aromatic system, the IR spectrum of the tropylium ion is remarkably simple (66MI2, p. 104; 73CRV293, p. 336). It consists of the C—H stretching vibration at  $3020\text{ cm}^{-1}$ , the C=C stretching vibration at  $1479\text{ cm}^{-1}$ , and a doublet at

678 and  $651\text{ cm}^{-1}$ , one peak of which is assigned to C—H out-of-plane bending (73MI2, p. 1592).

Such bending is also found in furotropylium ion **334** ( $763\text{ cm}^{-1}$ ; 67BCJ1480), together with a furan C—O stretching vibration at  $1052\text{ cm}^{-1}$ . Other heteroring bands are centered at about  $2500\text{ cm}^{-1}$  (broad NH) in pyrrolotropylum ion **335** (72CB1224) and at  $1660\text{ cm}^{-1}$  (C=N) in a corresponding triazole formed from tropone **111** (71CB1573). The C=N absorptions of 2-iminothiazoles **640a,b** (Scheme 172) were observed at about  $1640\text{ cm}^{-1}$  [94H(38)2691].

Cyclobutatropylium iron carbonyl complex **285** shows C=O bands at 2095, 2049, and  $2032\text{ cm}^{-1}$ , compared to 2044 and  $1980\text{ cm}^{-1}$  for the precursor tropyliene mixture **284** (78AJC1607). This shift to higher wave numbers is a result of increased back-bonding from iron to the cyclobutadiene ligand in the charged complex.

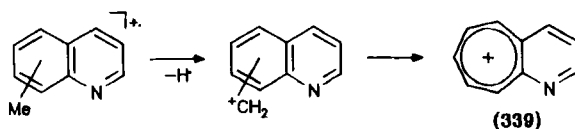
e. *Mass Spectrometry.* Generation of tropylium ions by ring expansion of benzyl-type compounds on electron impact is one of the most remarkable mass spectrometric results (73CRV293, p. 313; 94ACR138). In the case of heterocyclic rings fused to alkylbenzenes, the first fragmentation steps have also been rationalized in terms of ring expansion to give heterocyclotropylum ions, for instance, **339** [Scheme 87; 84CHEC(2)133; 85MI6].

### 3. Aromaticity and Stability

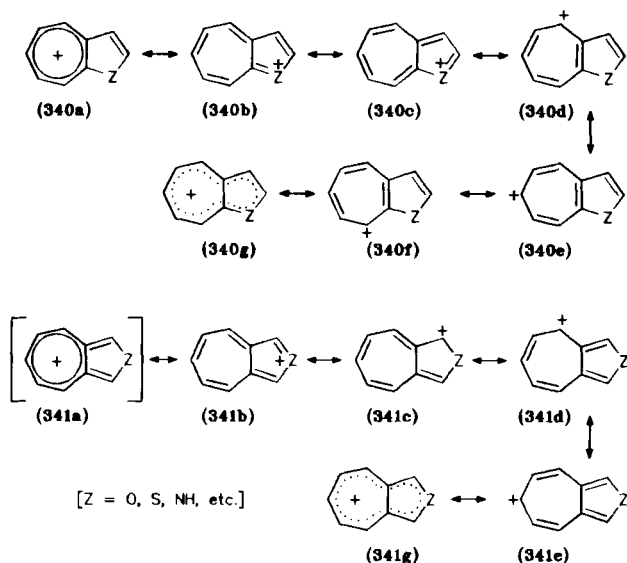
a. *Aromaticity and Mesomerism.* Regarding the parent tropylium ion, all of the physicochemical measurements, MO calculations, and labeling experiments are consistent with a structure having a planar aromatic ring of  $D_{7h}$ -symmetry (61MI1, p. 136; 73CRV293, p. 335, 73MI2, p. 1591).

In fused tropylium systems, however, different mesomeric forms are possible. Thus, heterocyclic [b]-fused compounds **340a** (= **3a**) are drawn in *Chemical Abstracts* (93MI1) in the heteronium form **340b** (Scheme 88); but for [c]-fused analogs **341b** (= **3b**), sometimes structures like **341a** were (incorrectly) used (81MI1; 84MI2, p. 86).

Furthermore, bis-fused tropylium ions like **342a** [e.g., **237**; 85HOU(5/2c)49, p. 71] have been depicted as carbenium ions **342b** [Scheme 89;



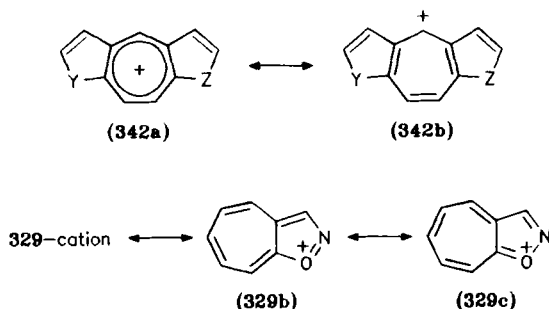
SCHEME 87



SCHEME 88

70ZC389; 72HOU(5/1d)301, p. 396; 73ACS2257] or **351** (Scheme 92; 78JHC285). The positive charge of cation **332a** is supposed to be distributed on carbon atoms 4, 5, and 6 (78T587).

In numerous investigations the charge distributions in fused tropylium ions have been estimated, especially by spectroscopic methods ( $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , UV-vis). In the case of thiophenes ( $Z = \text{S}$ ), for example, besides the "thienotropylium" ion (**340a**) and "thioniaazulenes" (**340b,c**; **341b**), several carbenium ("thiaazulenylum") ions (**340d-f**, **341c-e**) were taken into account (e.g., 67JOC1610; 69ZOR961; 74YZ1445).



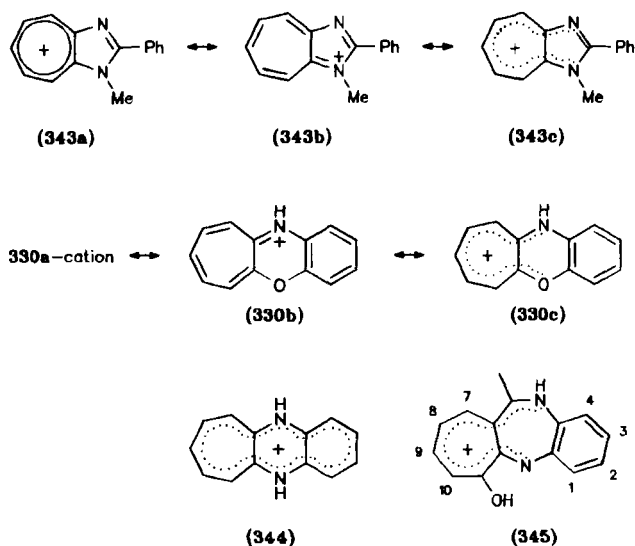
SCHEME 89

The structures of 6-hydroxyfuro[*c*]tropones like **336a** are expressed by polar forms analogous to **341b–e** (94TL8421). The cation structures of furan **218** (= **340a**, Z = O; 80TL3375) and isoxazole **329** (86CL1925), however, are best represented by the tropylium forms. Only a small amount of positive charge is located at the oxygen atoms, as in **340b,c** (Z = O) and **329b,c** (Scheme 89), respectively.

Mesomeric heteronium and carbenium forms are often graphically condensed to form closed electronic ring systems, as in **340g** and **341g** (e.g., 77BCJ3425; 80BCJ1461).

In the case of azolo- or azinotropylum ions, the resonance structures proposed include heteronium ions and open electronic systems (including the ring heteroatoms), as in imidazole **343a–c** (Scheme 90; 65CPB810) or in benzoxazines (**330b,c**) and benzothiazines (78BCJ2185, 78BCJ3316; 79BCJ3123; 85BCJ165; 89BCJ1158). In these cations the positive charge is not delocalized over the benzene ring, but a similar quinoxaline derivative **344** (= **252**) is thought to be a resonance-stabilized  $4n-\pi$  systems (cf. 73MI1, p. 223).

Furthermore,  $^1\text{H-NMR}$  spectroscopic results imply delocalization of the positive charge over the seven-membered rings of furan **258** (89JHC365), pyrrole **263** (75TL1849), diazepine **345** (81JHC335), and iron complex **285** (78AJC1607).



SCHEME 90

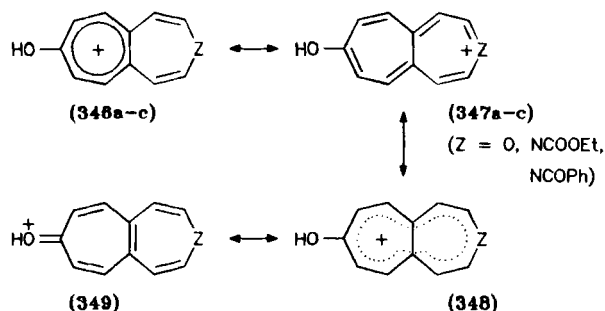
However, in oxepino- and azepinotropylium ions like **346a-c** (formed by protonation of tropones **156a,b**; Schemes 37 and 91) a contribution of onium forms **347a-c** is presumed (88CL1647; 90CL91), which decreases in the following order: **347a** > **347b** > **347c** > 4,5-dialkyltropone derivative. Moreover, the positive charge is believed to be delocalized over all parts of these molecules (including **348** and **349**; 92TL6487).

Tetracyclic pyrrole systems like **225** (Scheme 54), depending on the actual pH value, exist in an *N*-protonated azaazulenium form or in a pyrrolotropylium structure [89H(29)1655; 93TL835; 94JCS(P1)2721]. In a similar manner, both azaazulenium and pyrrolotropylium forms are derived from dicyclohepta[*b,d*]pyrrole **644** [see Scheme 173; 94JCS(P1)2579].

Pyrrole **335** is described as a resonance hydrid formed from structures charged at C-4b, C-8, or N-5 (72CB1224).

Mesomeric polar tropylium structures have been presumed or proved to exist in various seven-membered-ring compounds as a result of spectroscopic and chemical reactivity studies. Typical examples are 1-aza- and 1,3-diazaazulenes (62BCJ1188; 68BCJ2102; 89BCJ1133), tropobenzazines (84CL1145), "furano-*p*-benzoquinone tropides" like **613** (Scheme 164; 67BCJ1480), and certain pyrrolo-sesquifulvalene derivatives (bearing electron-acceptor groups in the cyclopentadiene moiety) like **396** (Scheme 105; 82CB3756). Other heteros-esquifulvalenes and related substances, however (e.g., **395**, Scheme 105), suggest little contribution of dipolar structures [70AG938; 78H(11)287; 79AP120].

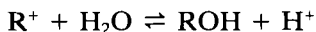
b. *Stability and Electrophilicity.* Investigations on stability revealed that even the stable monocyclic tropylium ion, having an acidity comparable with that of acetic acid, can suffer solvolysis and undergo reactions with added bases or even with its own anions if these are nucleophilic (73CRV293, p. 336; 73MI2, p. 1617; 84MI2, p. 74). Annulation of one, two,



SCHEME 91

or three benzene rings progressively diminishes the stability (73CRV293, p. 336; 84MI2, p. 85); a contradictory statement [85HOU(5/2c)49] is erroneous.

The stabilities of heterocyclic fused tropylium ions, expressed by their  $pK_{R^+}$  values, are listed in Table XXII. Increasing stability means decreasing electrophilicity or acidity. The definition of  $pK_{R^+}$  is usually derived (58HCA57; 67UK1721) from the equilibrium



and the equation

$$K_{R^+} = \frac{[ROH][H^+]}{[R^+][H_2O]}$$

The  $pK_{R^+}$  values of tropylium ions can be determined by potentiometric titration of dilute solutions with sodium hydroxide (the pH value at half-neutralization being taken as  $pK_{R^+}$ ), by measuring the initial pH values of aqueous solutions [71CR(273)160; 73ACS2257], by examining the UV spectra taken in various buffer solutions, or by polarography (70ZOB2078, 70ZOB2090; 86CL1925).

The following conclusions may be drawn from Table XXII and other data:

1. Whereas the stabilities of tropylium ions are diminished by benzo fusion (86CL1925), they are increased by isoelectronic thieno fusion [ $pK_{R^+}$ : **350a** (Scheme 92) < **220** < **221**; **290a** < **236b** < **221** < **238b**]. Thus, perchlorate **221** can be readily recrystallized from hot water (64JA5630; 65CCCC3016). However, isoxazole **327** is even less stable than benzotropylium ion (86CL1925).
2. Among thienotropylium ions, [c]-fused compounds are less stable than those of the [b]-series (e.g., **228a** < **220** < **221** and its homologs; 67ZOR191).
3. [b]-Fusion of a second thiophene ring onto thienotropone **221** in different positions yields increasing stabilities in the order **237b** < **332a** < **332b** (< **221**) < **238b**. [c]-Fusion of the second thiophene ring leads to unsymmetrical cations (e.g., **351**), which appear to be much less stable than their symmetrical analogs (78JHC285).
4. The stability is increased by changing to smaller chalcogen ring atoms ( $pK_{R^+}$ : **221** < **218**; **236c** < **236b**; **237b** < **237a**; **238b** < **238a**) or, especially, by changing from S to NPh ( $pK_{R^+}$ : **228a** < **228b**) (68ZOR907; 69ZOR2072; 74CCA243).
5. The stability of dibenzotropylium ion **290a** is decreased on complexation by  $Cr(CO)_3$  to form **290b**, in contrast to the behavior of benzylic carbenium ions (83AG572).

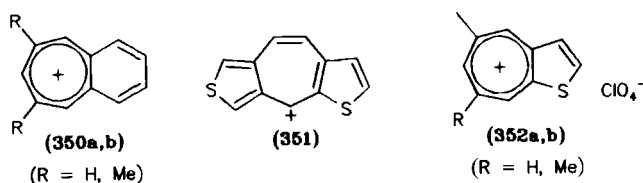
TABLE XXII

STABILITY OF TROPYLIUM IONS WITH FUSED HETEROCYCLIC RINGS (TYPES **333** AND **342**)

Fused ring <sup>a</sup>	Substitution or further fusion <sup>a,b</sup>	Formula no. <sup>c</sup>	pK <sub>R</sub> <sup>d</sup>	Reference
— <sup>e</sup>	—	<b>220</b>	4.75	84MI2, p. 85
benzene	—	<b>350a</b>	1.7	
	6,7-benzo <sup>f</sup>	<b>290a</b>	-3.7	
[b]furan	—	<b>218</b>	6.9	80TL3375
[b]thiophene	—	<b>221</b>	6.2	71CR(273)160
	5-Me	<b>352a</b>	6.7	
	5,7-di-Me	<b>352b</b>	7.2	
[c]thiophene	1,3,5,7-tetra-Me	<b>228a</b>	3.0	70ZOB2078
[c]pyrrole	2-Ph-1,3,5,7-tetra-Me	<b>228b</b>	8.0	70ZOB2090
[b]thiophene	[8,7- <i>b</i> ]thieno	<b>332a</b>	5.6	78T587
	[5,4- <i>b</i> ]thieno	<b>332b</b>	6.0	
	[6,5- <i>b</i> ]thieno	<b>237b</b>	5.4	70ZC389
	[7,6- <i>b</i> ]thieno	<b>238b</b>	6.65	
	[6,5- <i>b</i> ]furo	<b>237a</b>	6.8	73ACS2257
	[7,6- <i>b</i> ]furo	<b>238a</b>	6.9	
	6,7-benzo	<b>236b</b>	3.8	83CS(22)53
[b]selenophene	6,7-benzo	<b>236c</b>	3.4	

<sup>a</sup> See Table XIX, Footnote (b). <sup>b</sup> The numbering is that of the bicyclic system given in formula **333**. <sup>c</sup> Anions neglected. (For the measurements, as a rule, perchlorates or tetrafluoborates were used.) <sup>d</sup> Values taken in, or extrapolated to (**228a**), aqueous solution. <sup>e</sup> Parent tropylium ion. <sup>f</sup> Cr(CO)<sub>3</sub> complex (**290b**): pK<sub>R</sub> value = -6.3 [83AG(S)734].

The high stability of certain tropylium ions (e.g., **237** and **238**, in contrast to **351**) has also been demonstrated by spectroscopic observations (Section III,B,2,a-d) and by reactivity estimation (73ACS2257; 78JHC285). Thus, the facile formation and ready transformation of the corresponding tropones are explained by intermediates or mesomeric forms having a tropylium structure.



SCHEME 92



The increased stabilization upon thienoannulation as compared to benzoannulation may be caused by the more effective stabilization of the positive charge, by diminished angular ring strain, and by limited *peri* interactions between hydrogen atoms (due to the heteroatoms) and hence by nearly perfect planarity.

Certain syntheses of tropylium salts starting from tropylienes (Section II,B,1,a; Scheme 53) are characterized by the formation of more stable cations at the cost of less stable ones; they enable one to judge relative stabilities (73ACS2257).

As mentioned earlier, the stabilities of tropylium salts depend on the nucleophilicity of the anions. Compounds containing strongly nucleophilic anions are not (or are only feebly) dissociated, but exist as tropylienes (Section IV,B,3,b) or in tautomeric equilibria (cf. Section III,B,4; 67UK1721; 69ZOR2072; 73CRV293, p. 336; 84MI2, p. 74). The solvent dependence of  $pK_{R^+}$  values follows from measurements in aqueous-organic solutions containing ethanol or acetonitrile (69ZOB2601; 70ZOB2078, 70ZOB2090).

Quantum chemical calculations (HMO) of certain tropylium and related carbenium ions (64JA5630) show that a nearly linear relationship exists between  $pK_{R^+}$  and the "excessive"  $\pi$ -energy  $\Delta E_\pi$  (the difference between the  $\pi$ -electronic bond energies), where

$$\Delta E_\pi = E_\pi(\text{ROH}) - E_\pi(\text{R}^+).$$

A high gain in  $\pi$ -energy on going from the conjugated base (ROH) to the cation ( $\text{R}^+$ ) corresponds with a high  $pK_{R^+}$  value. This result is satisfactorily attained for thienotropylium ions **221** (64JA5630), **237**, and **238** (70-ZC389; 73ACS2257).

Furthermore, a topological approach was used (74CCA243) to explain the relatively small differences in the stabilities of the thienotropylium ions just mentioned and, by contrast, the drastic differences between this group and the benzo-fused tropylium ions.

#### 4. Tautomerism

Tropylium salts having nucleophilic anions (Section III,B,3,b) exist in tautomeric equilibria with their covalent species. Chlorination of hydroxytropylienes or tropones at their oxygen functionalities likewise leads to tautomeric equilibria of the corresponding chloro compounds (Section II,D,1,b). El'tsov *et al.* (69ZOR2072) studied the influence of anion exchange on the degree of ionization as determined by electronic spectrometry. In solutions of thieno[*c*]tropylium ions (e.g., the cation of **228a**) this degree increases along the series thiocyanate < chloride < bromide, which

corresponds with the increasing dissociation constants  $K_a$  of the respective acids.

Finally, diazepinotropylium ion **345** (81JHC335) is presumed to exist in the tautomeric 5H and 12H structures.

### 5. Polarographic Reduction

The polarographic reduction of the monocyclic tropylium ion in dilute aqueous solution shows a single, one-electron, irreversible reduction wave ( $-0.3$  V) (73MI2, p. 1596), as does the reduction of tetramethylpyrrolo[c]-tropylium salt **228b** (68ZOR907; 70ZOB2090). The half-wave potentials of several differently substituted derivatives of this salt are found within the limits of  $-0.15$  V and  $-0.41$  V.

Below pH 4, the polarograms of thieno[b]tropylium salt **352b** and analogous compounds consist of a single, one-electron reduction wave attributable to the formation of free radicals and their dimerization [71CR(273)160; 80CJC263]. Within the pH range from 4 to 7, a second wave appears corresponding to the formation of isomeric thienotropylidenes (by uptake of two electrons and one proton). The analogous [c]-fused thiophenes proved too unstable to be examined under these conditions.

In the case of thieno[c]tropylium salt **228a**, however, El'tsov and co-workers (70ZOB2078) succeeded in obtaining one or two one-electron waves at pH  $> 0.16$  or at pH 0.16, respectively. Above pH 0.52 the salt was hydrolyzed.

## IV. Reactivity

### A. TROPONES AND TROPOLONES

#### 1. General Remarks

The recognition, isolation, and characterization of troponoid systems have been facilitated by certain chemical properties (55CRV9; 68MI2; 73CRV293, p. 354; 78MI1; 84MI2, pp. 93 and 113), which usually occur in both monocyclic and fused derivatives.

Most *tropolones* give sparingly soluble, yellow or orange sodium salts, green cupric chelates, and colored ferric complexes. Although easily acetylated or methylated and frequently precipitated by picric acid, tropolones only exceptionally react with "carbonyl reagents." Electrophilic substitution reactions occur readily; however, sulfonation or nitration is inhibited

TABLE XXIII  
CALCULATED  $\pi$ -ELECTRON DENSITIES (HMO) OF TROPONES AND TROPYLIUM SALTS WITH FUSED HETEROCYCLIC RINGS

Fused heterocycle (position of CO)	Formula no.	$\pi$ -Electron density at C atoms										Reference
		1	2	3	3a	4	5	6	7	8	8a	
<i>A. Tropones</i>												
[b]furan (4)	<b>6a</b>	—	0.957	1.085	1.042	0.800	1.037	0.933	0.997	0.955	0.963	68MI1
(6)	<b>306a</b>	—	1.029	1.092	1.101	0.919	0.988	0.807	1.008	0.934	0.947	
[c]furan (6)	<b>307a</b>	0.974	—	0.974	1.067	0.908	1.073	0.793	1.073	0.908	1.067	68TL3771
		0.951	—	0.951	1.046	0.848	1.038	0.795	1.038	0.848	1.046	
<i>B. Tropylium salts</i>												
[b]thiophene	<b>221</b>	—	0.926	0.999	0.906	0.840	0.896	0.846	0.894	0.846	0.896	65CCC3016
[c]thiophene	<b>338</b>	0.935	—	0.935	0.963	0.792	0.952	0.796	0.952	0.792	0.963	
		1.021	—	1.021	0.999	0.800	0.975	0.810	0.975	0.800	0.999	68ZOR907
[c]pyrrole	—	1.021	—	1.021	0.998	0.796	0.970	0.807	0.970	0.796	0.998	

by the presence of sulfuric acid, which converts tropolones to their conjugate acids (dihydroxytropylium ions).

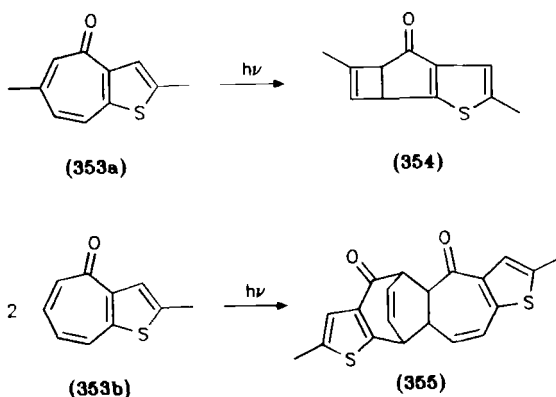
In contrast to many simpler analogs, most heterocyclic fused *tropones* easily form derivatives of the carbonyl group but seldom form picrates. Owing to the participation of tropylium oxide resonance structures, tropones undergo electrophilic substitutions much less readily than nucleophilic substitutions. Therefore, the *umpolung* of tropone has been investigated (88TL4723).

According to Nozoe [82PAC975; 90H(30)1263], the condensation of bi-functional nucleophiles with "reactive troponoids" (monocyclic tropones bearing a good leaving group of C-2) is not generally observed in the case of fused derivatives, for instance, of thieno- or pyridotropones. This fact has been explained in terms of the diminished aromatic character of the seven-membered ring (Section III,A,1).

The results of molecular orbital calculations on isomeric furotropones **6a** (Scheme 94), **306a**, and **307a** (Scheme 77) are presented in Table XXIII (Part A).

## 2. Photochemical Reactions

Valence isomerization and dimerization are common reactions in the photochemistry of troponoids [61MI1, p. 152; 71PAC239, p. 254; 73CRV293, p. 358; 84MI2, p. 103; 85HOU(5/2c)710, p. 751]. G. Jones *et al.* [77JCS(P1)505] found both transformations on irradiating different thienotropones **353** (Scheme 93).



SCHEME 93

The 2,6-dimethyl derivatives **353a** gives the tricyclic ketone **354** resulting from an intramolecular electrocyclic reaction. However, the parent thienotropone (**51**) and its 2- (**353b**) or 7-methyl derivatives give [4 + 2] dimers (e.g., **355**) of the head-to-head type. These dimers are formed by reaction of the 5,6-ene bond of one molecule with the 5,7-diene system of another. The dimerization seems to be the normal photochemical reaction of this group of thienotropones and to be suppressed by a 6-methyl substituent (e.g., in **353a**).

In similar experiments, furotropone **6a** (Scheme 94), pyrrolotropones, indolotropones, and pyridotropones (e.g., **304** and **356**) on irradiation gave only polymeric materials [84JCS(P1)2297]. Presumably only the thienotropones **353** exhibit the proper combination of increased electron density on the seven-membered ring and stability of the heterocyclic ring to form defined photoproducts.

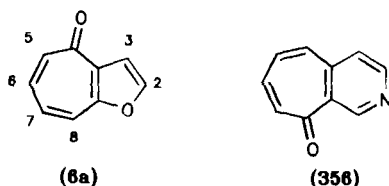
Oxepinotropones like **147b**, in contrast to 1-benzoxepines, do not undergo photoinduced intramolecular cyclization [94H(38)957].

### 3. Acidity and Basicity

a. *Acidity.* The acidity of parent tropolone ( $pK_a$  7.0) lies between those of acetic acid (4.8) and phenol (10.0); benzotropolones are only as acidic as phenol (55CRV9).

Likewise, the  $pK_a$  values of furo- and thienotropolones **308–310** (Scheme 77) lie in the range 9.10–9.90 [71CR(237)160; 82AC(R)191]. Naturally, indolotropolone **301** is also less acidic than tropolone; it does not dissolve in bicarbonate solution [57LA(608)38]. Finally, the protolytic equilibria of thienotropolone **308b** in homogeneous solutions and in aqueous micellar systems of surfactants were investigated [89SA(A)803].

Tautomeric azaazulenones show different behavior. Pyrrolotropone **303b** is insoluble in alkali but gives a crystalline hydrochloride (54MI2), whereas imidazotropones **15** and **16** dissolve in acid and in alkali (62BCJ1188).



SCHEME 94

b. *Basicity.* Parent tropone forms very stable salts with acids; its basicity has its origin in the high stability of the hydroxytropylium ion formed by protonation. Most substituted tropones and in particular the tropolones are less basic (55CRV9; 73CRV293, p. 327).

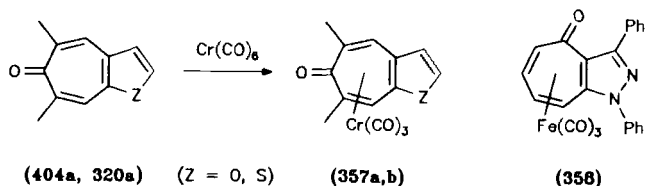
In concentrated sulfuric acid, the less aromatic furo[*c*]tropone **307a** was found to be protonated predominantly at the carbonyl oxygen (68T4501). The basicities of the corresponding thieno[*b*]- (**306b**) and thieno[*c*]tropones (**307b**) were determined to be similar to those of pyridine and tributylamine, respectively (74JCPB93). *O*-Protonation of fused tropones is a common route to obtain tropylium salts (Section II,C,1,d).

An example of a sufficiently basic fused tropolone is that of anhydrosepe-donin (**169**), which forms a hydrochloride and a hydroperchlorate, both being stable under anhydrous conditions (65CJC1835).

c. *Complexation.* Chelate complexes of tropolones have already been mentioned (Section IV,A,1; 55CRV9; 56MI2, p. 448; 73CRV293, pp. 322 and 342). Moreover, metal  $\pi$ -complexes of tropones are well known (73CRV293, pp. 319, 339, and 362). Thus, ligand replacement has been employed for the synthesis of furo[*b*]- and thieno[*b*]tropone chromium tricarbonyl complexes **357** [Scheme 95; 78JOM(148)277]. (The reaction is not applicable to [*c*]-fused isomers.) Furan complex **357a**, according to the X-ray crystallographic determination, possesses the same structural arrangement as analogous arenetropone complexes [78AX(B)-1714].

The mass spectrometric fragmentation of these complexes [80PS(9)165; 94RRC41] is characterized by successive loss of three carbonyl groups, followed by elimination of chromium and further fragmentation in the manner shown by the organic ligands (Section II,A,2,e).

Iron tricarbonyl complex **358** is the main product (besides **143d**, etc.) in an incomplete oxidation of the regioisomeric dihydro derivatives by cerium(IV) [Section II,A,3,h, third paragraph; 77JCS(P1)939].



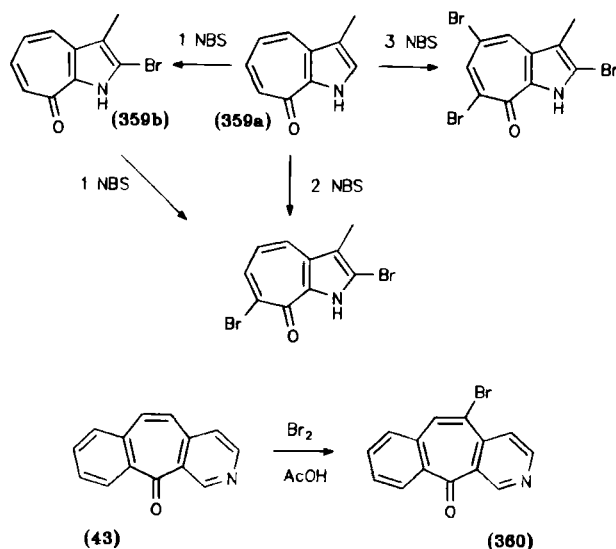
SCHEME 95

#### 4. Reactivity at the Seven-Membered Ring

a. *Electrophilic Reactions at Ring Atoms.* Parent *tropone*, on halogenation, affords addition products and, by subsequent dehydrohalogenation, halotropones substituted at 2- or 2,7-positions (66MI2, p. 134). If pyrrolotropone **359a** is treated with *N*-bromosuccinimide (NBS), the ring atoms are attacked by bromine in the order C-2 > C-7 > C-5 (Scheme 96; 61YZ1799). Logically, bromine enters indolotropone **56b** (R = H) at the 7-position (75BCJ314).

However, pyrrolotropone **303b** and furotropone **100** resist bromination or other electrophilic substitutions, respectively (54MI2; 65BCJ301). No deuterium exchange was observed on treating furoxanotropone **326** with deuterated trifluoroacetic acid/sulfuric acid, probably because of protonation at the carbonyl oxygen, which prevents further reaction (74JOC2956).

Certain tricyclic tropones like pyridine derivative **43** can be brominated to give monobromo compounds (e.g., **360**) directly, presumably through an addition-elimination mechanism (85JHC555). Other substances exhibit more olefin-like behavior (like that of tropone; see above), so that dehydrohalogenation must be accomplished by DBU (90JOC3341) or KOH (formation of **8** from **7**; 76HCA866). Some dibromides are stable (82JHC967). A related indolotropone is brominated in both the tropone and the benzene rings (72BCJ269).



SCHEME 96

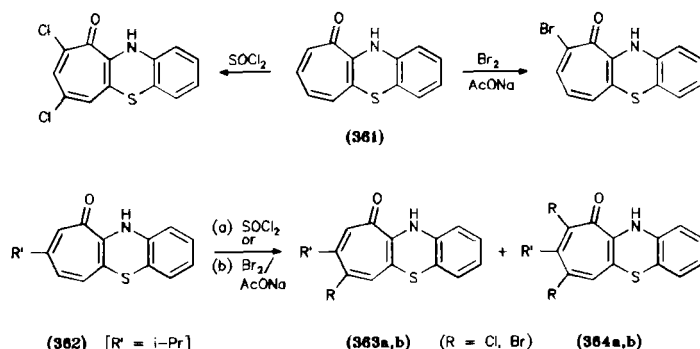
The halogenation of benzothiazinotropones **361** and **362** as depicted in Scheme 97 affords 7- and/or 9-substituted derivatives like **363** and **364** (66BCJ1980). Chlorination of **362** additionally gives the 9-chloro compound or, on treating the tropone with thionyl chloride in excess (2.5 molar equivalents), a 7,9,*x*-trichloro derivative, presumably substituted at the benzene ring.

The nitration of the same substrates, in addition to the 7-nitro derivative (**305**) of **361**, yields sulfoxides and nitrosulfoxides. These reactions as well as the bromination and nitration of sulfoxides and sulfones (66BCJ1988) are dealt with in Section IV,A,5,b (Schemes 121–123).

The oxidation by alkaline hydrogen peroxide converts tropones into epoxy derivatives (84MI2, p. 92). Some thienotropones or their sulfones, on oxidation by *m*-chloroperbenzoic acid, give mono- or bis-epoxides, for instance, the stable compound **461** (Section IV,A,5,b; Scheme 124; 84BCJ3156). Another example is that of tetracyclic **372** (Scheme 99), formed from cycloheptabis[1,2,5]thiadiazol-7-one (89BCJ2421); its transformation into the desired tropolone failed. Finally, autoxidation of pyranotropone **634** gives unstable endoxide **636** (see Scheme 171; 94BCJ2803).

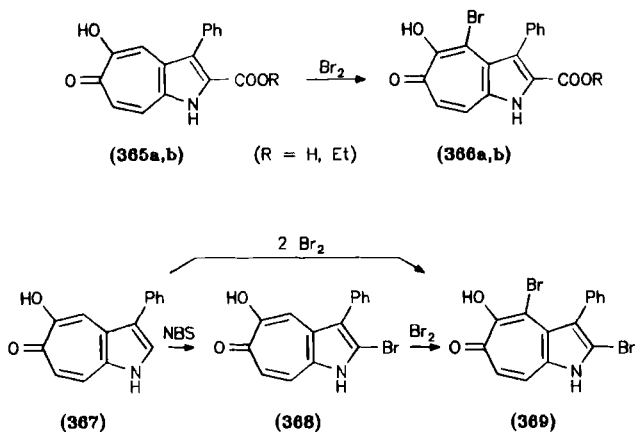
With monocyclic *tropolone*, electrophilic substitutions preferentially occur at the 5-position. One major exception to this rule is halogenation, which takes place at C-3 and then at C-7 (55CRV9, p. 40). In fused derivatives, aside from the heteroring, the positions vicinal to the oxygen functionalities are preferred.

Thus, 5-hydroxycyclohepta[*b*]pyrrol-6-one derivatives having occupied (**365**) or vacant (**367**) 2-positions are brominated at the 4-position (**366**) or 2- and 4-positions (**368**, **369**), respectively (Scheme 98; 63CPB1440). Nitration of tropolone **365b** again takes place at C-4 to give **548b** (63CPB1431).



SCHEME 97

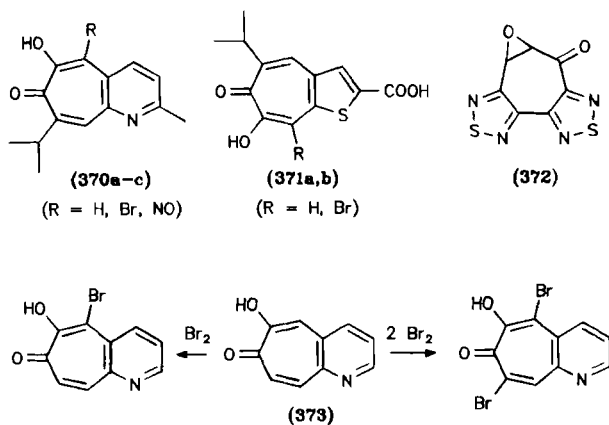




SCHEME 98

Structurally related 6-hydroxycyclohepta[*b*]pyrid-7-one derivatives like **370a** (Schemes 99 and 144) are analogously brominated (60NKZ295; 61BCJ42) or nitrosated (59NKZ1175) in the 5-position to give, for example, compounds **370b** and **c**, respectively. In the same tropolone system a vacant 8-position (in **373**) is occupied by a second bromine atom; further bromination leads to 5,5-di-bromo- and 5,5,8-tribromo-6,7-dicarbonyl structures (65MI3).

Finally, 7-hydroxycyclohepta[*b*]thiophen-6-one **371a** is brominated at the 8-position (to give **371b**); its nitration is accompanied by decarboxylation and attack at C-2 and C-8 (62BCJ808).



SCHEME 99

b. *Nucleophilic Reactions at Ring Atoms.* Relevant types of nucleophilic *substitutions* in tropones, according to Nozoe's and Pietra's generalizations (59MI1, p. 407; 79ACR132), are the following:

1. substitution of hydrogen;
2. displacement of a substituent by a new one (*ipso* substitution; Section IV,A,4,e);
3. introduction of a new substituent onto a neighboring position (*cine* substitution; Sections II,B,1,f and IV,A,4,e);
4. skeletal rearrangement reactions (Section IV,A,7,d).

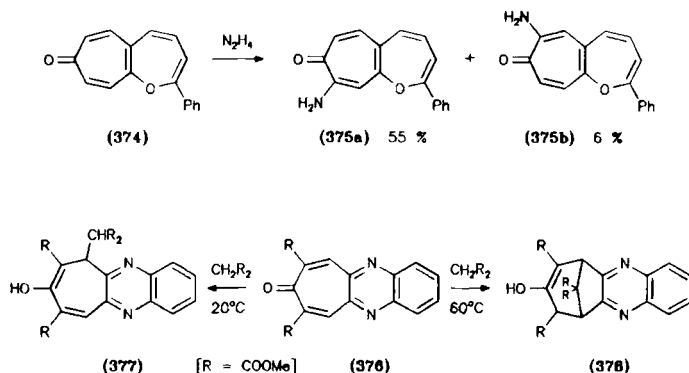
The reactions of tropone with hydroxylamine or hydrazine yield 2-aminotropone (59MI1, p. 415), in the first case admixed with troponeoxime (Section IV,A,8,b). Besides nucleophilic substitution, an additive mechanism was discussed (66MI2, p. 135; 73CRV293, p. 354).

Just like tropone, oxepinotropone **374** (Scheme 100) with hydrazine gives the 9-amino compound **375a** (and a small amount of the 7-amino isomer **375b**), whereas treatment with hydroxylamine leads to **375a** and the *E*- and *Z*-forms of the oxime [94H(38)957].

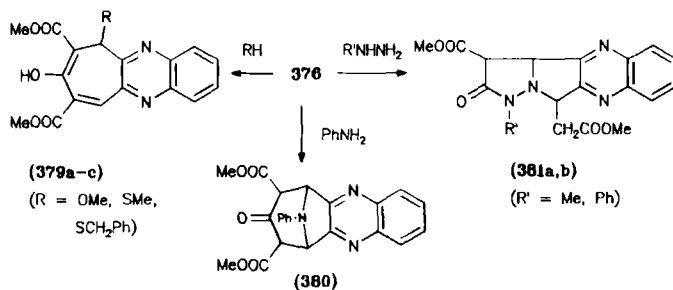
In the field of nucleophilic *additions*, Quéguiner and co-workers investigated Michael-type additions onto quinoxalotropones like **376** (Schemes 100 and 101; 83CJC1806) whose electrophilic sites are C-6, C-10, and C-8. The reactions lead to 1,4-monoaddition products or to bridged compounds resulting from bis-1,4-addition reactions:

1. Among carbon nucleophiles, diethyl malonate gives adducts **377** and **378**; malononitrile, even at 20°C, gives an analog of **378** (with R = CN); and diethyl acetonedicarboxylate yields a bridged diketotetracarboxylate.

2. Oxygen and sulfur nucleophiles (methoxide and mercaptans) always form monoadducts at C-6 (**379a-c**).



SCHEME 100

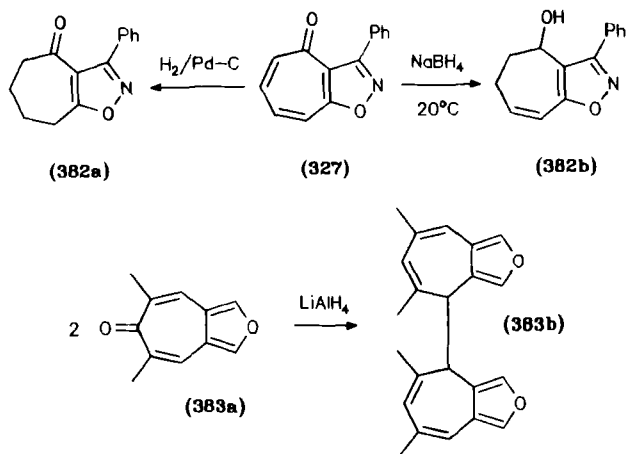


SCHEME 101

3. Among nitrogen nucleophiles, aniline affords a bridged bis-adduct (**380**). After treatment with hydrazines, analogous intermediate adducts are postulated that suffer ring rearrangement to give tetracyclic compounds **381**.

Catalytic *hydrogenation* of bicyclic tropones generally affords tetrahydro derivatives like **382a** (74T3765). Analogous products are obtained from pyrazoles **143** [72TL1925; 75JCS(P1)939], imidazoles (93MI3; 94MI3), triazoles (54MI1), and from indolotropones **56** (75CPB2818).

In pentacyclic derivatives, e.g., **53** one double bond is hydrogenated (64JCS5096; 92T5481; 96T1707). (The carbonyl group in pyrrole **53b** is not attacked, even by lithium aluminum hydride). In the case of certain pyrroles [76H(4)969] and of quinoxaline **27** (58MI2), mixtures of tetrahydrotropones and tetrahydrotropols are isolated. The tropone ring of **27** is also reduced



SCHEME 102

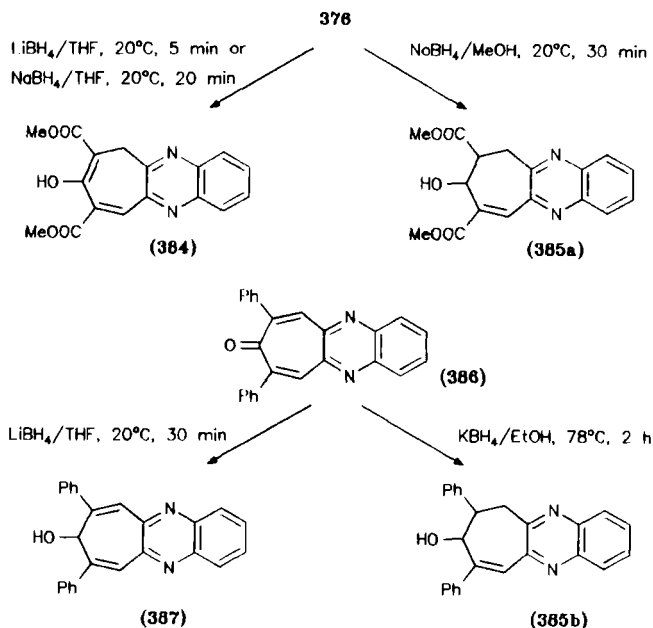
by hydrazine. Anhydrosepedonin (**169**) is perhydrogenated in the presence of platinum dioxide (71ABC862).

*Reduction* by complex hydrides gives different results depending on the reagents and the conditions chosen. Unexpectedly, furotropone **383a** yields dimer **383b** [77BSF(2)75].

Again, Quéguiner and co-workers (82T3043; Scheme 103) investigated the regioselectivity of the reduction of quinoxalotropones **376** and **386**. Applying varied hydrides and conditions, they obtained tropols **384** and **387** or dihydrotropols **385a,b**, as well as deuterated derivatives. [In analogy to **385a**, isoxazole **382b** is formed from **327** under similar conditions (86CL1925).]

The reduction mechanism was elucidated by calculating the electronic structures (*ab initio* STO 3G method) of the possible complexes and by comparing them to the  $\alpha$ -enone structures. Thus it was demonstrated that these tropones are reduced under frontier orbital control and that carbonyl complexation by the alkali cations is essential.

*c. Reactivity of the Troponoid Carbonyl Group.* In strong acids the carbonyl group is *protonated* to give hydroxytropylium ions (Section II,C,1,d).



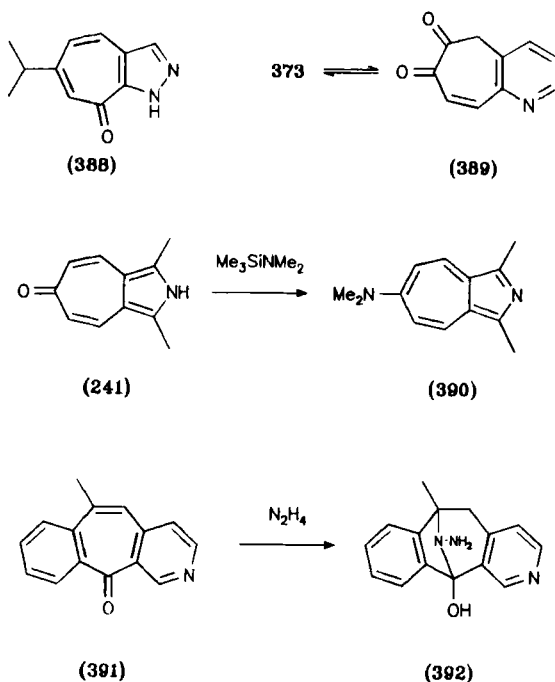
SCHEME 103

Favored by their less aromatic character, a majority of fused tropones condense with “ketonic reagents” like phenylhydrazines to form troponeimine derivatives (Section IV,A,8,b). Exceptions include furo[*b*]tropone **100** (65BCJ301); tautomerizable pyrrolo- and pyrazolotropones **303b**, **388** (Scheme 104), and **53b** (54MI2; 58MI1; 64JCS5096); and sterically hindered pyrazolotropone **86b** (80JHC1293).

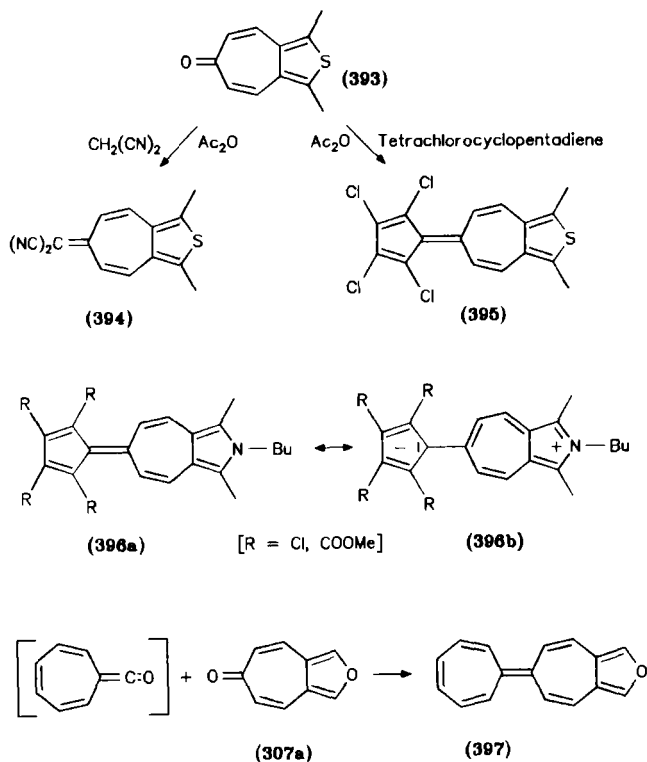
The tropolone carbonyl group does not give ketonic derivatives unless the aromaticity of the ring is much decreased, as in some benzo-fused tropolones (68MI2, p. 370). Pyridotropolones like **373** (65MI3), apparently having a 1,2-diketone structure (eventually **389**), afford dioximes, dihydrazones, osazones, and quinoxalines (Section IV,A,6,a). Their methyl ethers show the normal tropone reactivity.

The reactions of tropones with phosphorus pentasulfide and amines to give, respectively, *trophothiones* or *troponeimines* (including reductive amination) are treated in Section IV,A,8,a and b.

Tautomerizable pyrrolotropone **241** can be *aminated* by silylamines, but the resulting 6-aminoazaazulenes like **390** are extremely unstable (84S119). Treating benzopyridotropones of the **391** type with hydrazine generates



SCHEME 104



SCHEME 105

*N*-aminated end-imino (imino-bridged) compounds like **392** (86JHC1331). These products result from the addition of the reagent to the keto group without dehydration, followed by regiospecific cyclization of the secondary amino function into the vinylene group.

The condensation of *active methylene compounds* with tropones (Scheme 105) is exemplified by reactions of malonic dinitrile (70AG938; 78CZ404), methyl cyanoacetate [92CL1453; 93H(36)1725; 94MI2], cyclopentadiene or cyclopentenedione derivatives (70AG938; 79AP120; 82CB3756), and dimethylbarbituric acid (76CZ142) using the "anhydride method." Thus, heptafulvene **394** and sesquifulvalenes **395** and (noticeably polarized) **396** are obtained. Alternatively, tropones can be activated for this reaction by transformation into 6-substituted tropylium salts (Section IV,B,3,c).

Another synthetic route consists in the condensation of cyclic ketenes (8-oxoheptafulvene, diphenyleneketene) *in situ* with furotropones **6a** or **307a** to yield hepta- (**397**) and sesquifulvalenes [78H(11)287].

The methylenation of the carbonyl groups in tropones **398a** and **398b** (= **9**) proceeds via Wittig or Horner–Emmons reactions (Scheme 106) to give **399a** and **400b**, respectively (80EUP11206; 90HCA1197).

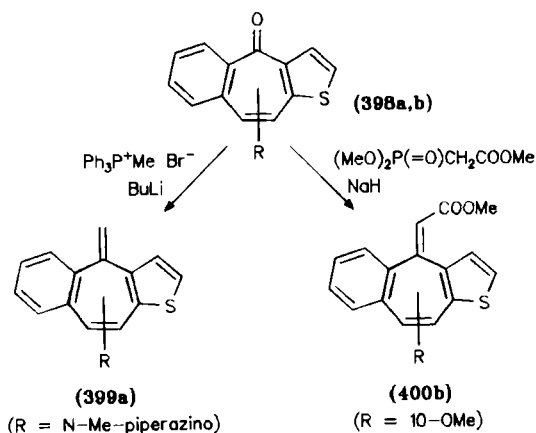
The *reduction* of tropones by sodium or potassium borohydrides (72AF133; 78PJC2045) or lithium aluminum hydride leads to tropols, whereas many bis-fused tropones [e.g., **398b** (85JHC1205) and **234**] are transformed into tropylenes by  $\text{LiAlH}_4/\text{AlCl}_3$  (sometimes even without  $\text{AlCl}_3$ ). These are two important routes to precursors of tropylium salts (Section II,C,1,c). Pyrazolotropone **406** (Scheme 108) resists reduction by complex hydrides [72JCS(P1)1623].

Pyridotropone **401** (Scheme 107) is converted to tropyliene **402** by the Wolff–Kishner reduction (72JMC750), which, however, fails in the case of enol ether **398b** (85JHC1205).

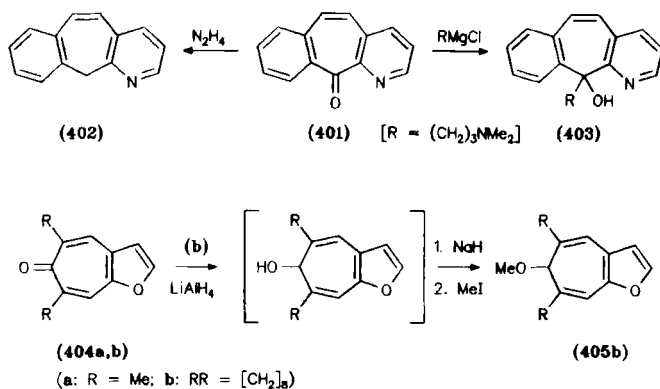
The reduction of *ansa*-troponone **404b** affords a nonisolable tropol that can be alkylated to methoxytropyliene **405b** (85MI3).

The addition of *organometallic compounds* onto tropones initiates another useful path to tropylium salts (Section II,C,1,c). Further examples include the reaction of tropones **360** and **391** (85JHC555; 86JHC145) or **401** (to yield **403**; 72JMC750) with alkyl, aminoalkyl, or aryl Grignard compounds; or that of pyrazolone **406** (Scheme 108) with phenyllithium to give tropol **407** [72JCS(P1)1623]. The Reformatsky reaction (zinc and ethyl bromoacetate) can also be used (68USP3366635).

On treatment of monocyclic tropones with organometallics, usually C-2 and C-7 are attacked by the carbanion much more rapidly than the keto carbon atom (59MI1, p. 421; 73CRV293, p. 354). Heterocyclotropones, however, nearly always react “normally” (1,2-addition onto the carbonyl).



SCHEME 106

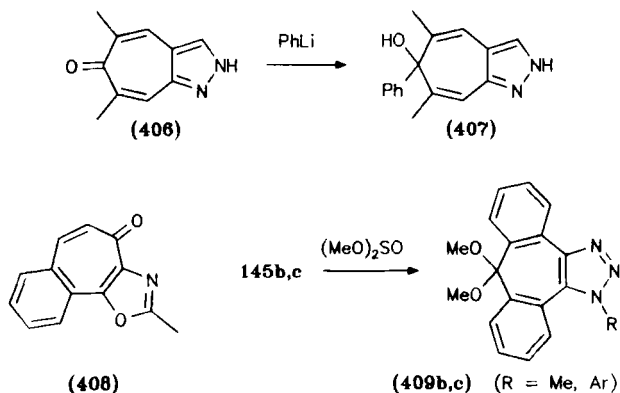


SCHEME 107

Exceptionally, both 1,2- and 1,4-addition occur on the reaction of thienotropone **231** with phenyllithium (Scheme 56; Section II,C,1,c; 74YZ1429) and reaction of oxazotropone **408** with 1-methyl-4-piperidinomagnesium chloride (74JMC1316).

*Troponeacetals* (e.g., **409**) are formed, by means of dimethyl sulfite, from tetracyclic triazoles (**145**) or pyrazine [67LA(705)169], whereas mercaptalization of thienotropones by ethane-1,2-dithiol fails [85JCS(P1)983].

*Chlorination* of tautomerizable, nitrogen-containing heterocyclic fused tropones at their oxygen functionalities by phosphorus oxychloride transforms them into chloroazaazulenes or chlorotropazines. Thus, pyrrolotropones like **303b** (54MI2; 77BCJ1184) and pyrazolotropone **388** (58MI1)



SCHEME 108



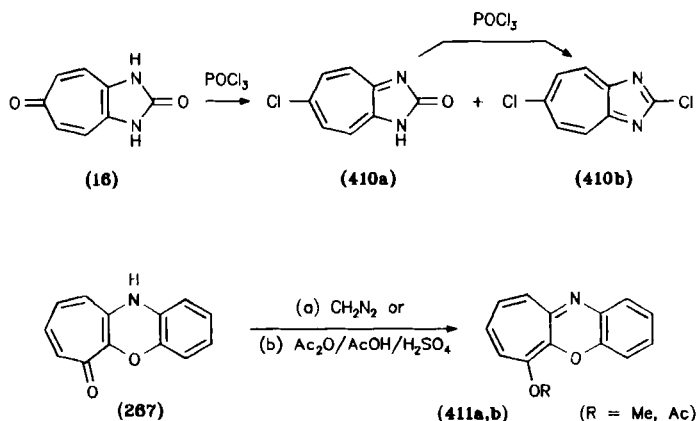
give 8-chloro derivatives. Indolotropone **56b** ( $R = H$ ) is transformed into 6-chlorobenzazaazulene (75BCJ314; 76BCJ1101).

The successive attack onto CO-6 and CO-2 of imidazotropone **16** to give chlorodiazaazulenes **410a** and **b** (Scheme 109; 62BCJ1188) corresponds with the lower electron densities at the carbon atoms of the seven-membered rings. Similarly, pyrrolotropones **126b/127/435** and **181** form 2,8- and 2,5-dichloro compounds (e.g., **481** and **483a,b**), respectively (Scheme 128; 62YZ418; 65BCJ306).

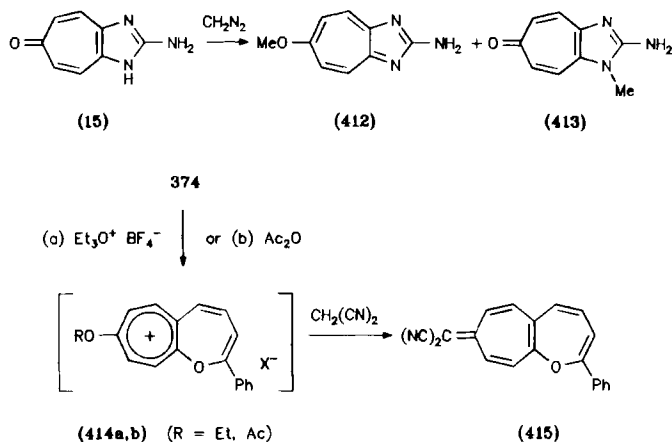
Thionyl chloride is also reported to transform tropones into chloroazaa-zulenes (66BCJ1980; 75BCJ314). In the cases of benzothiazinotropones **361** and **362** (Section IV,A,4,a; Scheme 97), however, it effects electrophilic chlorination without attacking the carbonyl or tautomeric enol groups (66BCJ1980). Geminate dichlorination at the carbonyl groups of pyrrolo[c]tropones **264** yields tautomeric compounds **265/266** (Section II,D,1,b; Scheme 66).

*O*-Alkylation and *O*-acylation of tautomerizable fused tropones (e.g., by diazomethane or acetic anhydride) lead to alkoxy- or acyloxytropylienes, respectively. Thus, four of the isomeric benzoxazinotropones (except for the 10-oxo isomer) yield ethers and esters; for example, tropone **267** gives derivatives **411a** and **b** (91BCJ2131).

Similarly, the 8-isopropyl homolog of "β-tropone" **181** can be transformed into the 5-acetoxy compound (67MI1), and imidazole **15** (Scheme 110) yields the products of *O*- and predominant *N*-1-methylation, namely **412** and **413** (62BCJ1188). Furthermore, the carbonyl groups of pyrrole



SCHEME 109



**SCHEME 110**

**303b** and furan **104b** are methylated (67CPB634; 71PAC239, p. 265); that of pyrrole **241** is ethylated by triethyloxonium tetrafluoroborate to give tropylium salt **242** and, after deprotonation, affords the corresponding 6-ethoxy-2-azaazulene (75AG840). On benzylating pyrrole **435** (Scheme 118) at carbon and nitrogen, benzyl ether **438b** is obtained (65CPB473) in a side reaction.

Analogous reactions of nontautomerizable tropones offer a route to tropylium salts (Section II,C,1,d). Generally, the carbonyl group of tropone can be activated in this way (68MI2). Thus, oxepinotropone **374** is condensed (Scheme 110), via nonisolable tropylium salts **414a** and **b**, with malonitrile to form heptafulvene **415** [94H(38)957].

d. *Reactivity of the Tropolone Hydroxyl Group.* Tropolones may be regarded as vinylogous carboxylic acids; their *O*-alkyl and *O*-acyl derivatives are vinylogous esters and anhydrides and can be best prepared by means of diazomethane (or dimethyl sulfate) and acetic anhydride, respectively (59MI1, p. 382; 73CRV293, p. 360; 84MI2, p. 112).

In contrast to unsymmetrically substituted monocyclic tropolones (which usually give two isomeric derivatives), both benzo- and heterocyclotropolones form only one product, owing to the resonance inhibition of the tropolone ring.

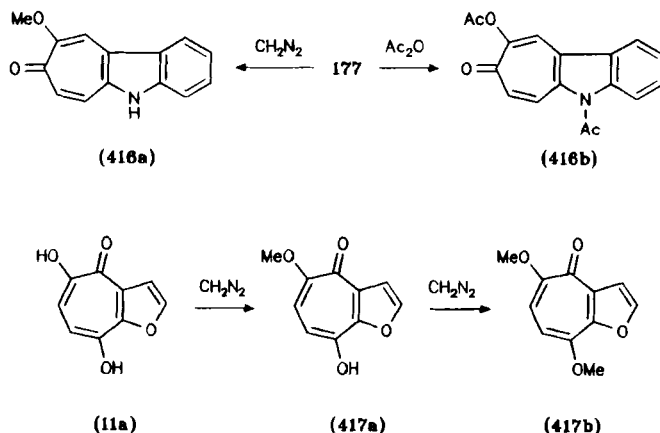
Examples of *O*-acetylation, *O*-tosylation, and *O*-methylation are those undergone by tropolones **210** (R = H), **83**, and **308b**, respectively [52CI(L)471; 65BCJ362; 71BSF1437]. Moreover, with nitrogen-containing heterocyclic analogs, sometimes *N*-substitution is observed (66BCJ253;

72BCJ226). Thus, indole **177** gives *O*-methyl derivative **416a** and *O,N*-diacetyl compound **416b** (Scheme 111). Isomeric tropolone **301**, showing "anomalous behavior of tropolones," resists methylation [57LA(608)38; 70JPR(312)466].

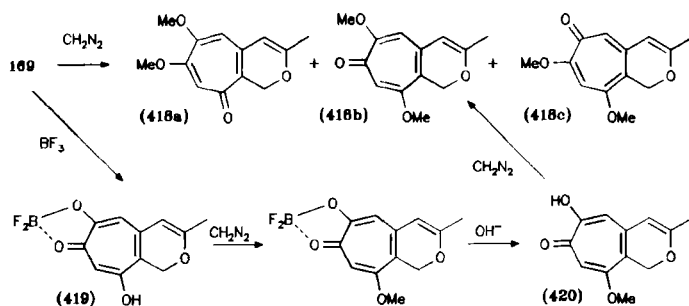
Bistropolonofurans like **159** or **162** yield *O,O'*-bismethyl or -bisacetyl compounds (51MI1; 54JCS286; 82CL701; 83CL1371; 85BCJ515). Starting from hydroxytropolone **11a**, on methylation by steps, ethers **417a** and **b** are obtained (54CB1197). Hydroxytropolone **169** (Scheme 112), however, having a fused nonaromatic heterocyclic ring, gives three isomeric dimethyl ethers **418a-c** (65CJC1835; 69MI3; 72CJC821). Its selective monomethylation at the 9-position to afford **420** succeeds via difluoroboron complex **419** in which the oxygen functionalities of tropolone are protected.

Chlorination of the hydroxyl group to give 2-chlorotropolones, as known from the parent tropolone (59MI1, p. 423), was not observed in the case of pyridotropolone **373** (65MI3).

e. *Reactivity of Other Nuclear Substituents.* Tropone substituted at the 2-position by alkoxy, acyloxy, halogen, or amino groups are both tropolone and (vinyllogous) carboxylic acid derivatives (esters, anhydrides, halides, or amides) that exhibit the reactivity of the latter (55CRV9, p. 92; 56MI2, p. 445; 68MI2). In the monocyclic series, they readily undergo *hydrolysis* or other nucleophilic substitutions (unless they suffer ring contraction; cf. Section IV,A,7,d). Similarly, such groups are substituted at other positions, especially under acidic conditions (55CRV9, p. 55; 66MI2, pp. 136 and 145; 73CRV293, p. 344).



SCHEME 111

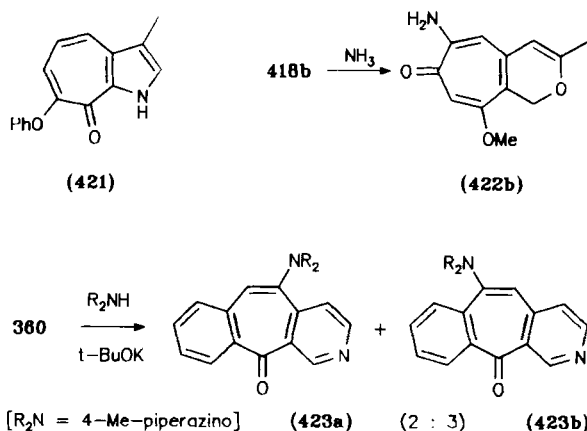


SCHEME 112

Methoxy- and chlorobenzotropones are less reactive [56FOR(13), p. 269; 66MI2, p. 152]. In the heterocyclo-fused series, however, most tropolone ethers are cleaved by sulfuric acid (70JA6382), hydrochloric acid (85BCJ515), or (preferentially) hydrobromic acid to give tropolones (Section II,A,1,d). Tropolone acetates (54JCS286) and methoxytropone **9** (77GEP2625642) are also hydrolyzed, but phenyl ether **421** (Scheme 113; 63MI1) and the methyl ether of pyridotropolone **373** (65MI3) resist hydrolysis or other nucleophilic reactions.

*Amidation* of anhydrosepedonin dimethyl ethers (**418b,c**) by liquid ammonia leads to isomeric 2-aminotropones like **422b** (69MI3).

The following examples illustrate the *displacement of halogen* by oxygen-, sulfur-, or nitrogen-containing substituents and the exchange of halogen:



SCHEME 113

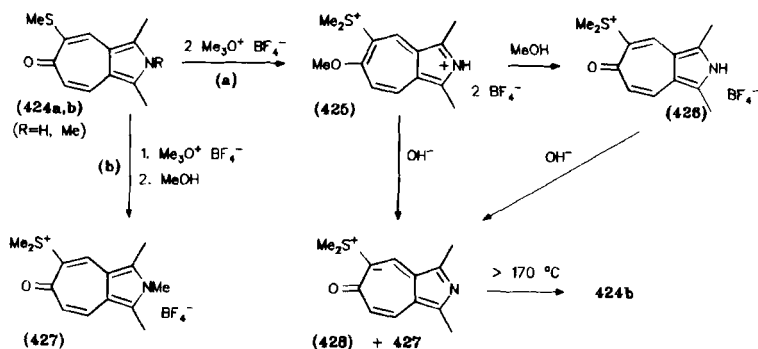
1. Hydrolytic cleavage of bromine in pyrrolotropolone **366a** occurs on heating in aqueous ammonia (63CPB1440). The 7-bromo derivative of indole **56a** ( $R = H$ ), however, is stable even when treated with concentrated mineral acids or sodium methylate (75BCJ314).
2. Bromine at C-9 in dibromoquinoxalotropone **118c** is replaced by the 2-aminophenylthio residue to give **552** [Scheme 146; 89H(29)1459].
3. The aminolysis of brominated thieno- (**8**) and pyridotropones (**360**) gives isomeric enamines **398a** or **423a,b**, respectively (76HCA866; 85JHC555). Minimal regioselectivity signifies dehydrotropone intermediacy. Similarly, amination of 5-bromofurotropone **6b** by isopropylamine to give 6-amino derivative **321** (Scheme 81) proceeds through a cine substitution reaction [80JCS(P1)2081].
4. Bromine-chlorine exchange with pyrazolotropones is rapid in the case of dibromide **142** [by HCl/methanol, substitution of one bromine atom (66BCJ253)], but exchange proceeds slowly and incompletely with a 5-bromo compound [by acetyl chloride/acetic anhydride (61MI2)].

*Dehalogenation* can be achieved either by nascent hydrogen (zinc/acetic acid) to get oxazine **297** from **118a** (91BCJ2131) or, preferably, by catalytic reduction over palladium-charcoal (62MI1; 66BCJ253). Thus, bromine from the tropone  $\alpha$ -position or from more remote sites is eliminated to give furotropone **100** [65BCJ301; 73JCS(P1)1960], pyrazolotropones **98a** ( $R = i\text{-Pr}$ ) and **388** (58MI1), and furoditropolone **159** (82CL701). Furthermore, debromination can occur on reducing tropones by complex hydrides (89CCCC2443).

Among the *transformations of individual substituents*, hydrolysis of carboxylic esters followed by thermal decarboxylation is used for degradation and structural elucidation. Common procedures for decarboxylation include catalysis by copper in quinoline (83JPR853) and the melt (80JHC93) or decomposition of silver salts in an atmosphere of hydrogen at about 200°C (73JHC1075, 73JHC1083). By the copper catalytic method, thiophene **306b** (71BSF1437), pyrrole **241** [76H(4)969], and pyrazole **323** (72JOC676) are obtained. Thiophene **393** is formed by heating its dicarboxylic acid in hydrochloric acid solution (69ZOR570).

Both hydrolysis and decarboxylation are accomplished by hydrochloric acid [to get, after 60 hours, pyrrole **241** (75AG840)] or by trifluoroacetic acid/hydrochloric acid [to degrade dicarboxylic ester **302a** (82CZ411)]. However, certain dicarboxylic acids resist decarboxylation (88AP757) or give poor yields of the parent compounds; this is seen, for example, in the case of furan **307a** (68T4501).

The *amino derivative* **516a** (Scheme 135) was prepared by catalytic hydrogenation of nitrosotropolone **370c** (59NKZ1175). Similarly, amino (and



SCHEME 114

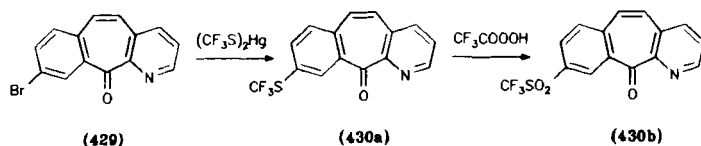
acetamino) compounds can be obtained from nitro tropenoids, for instance, from oxazoles (59MI3), from thiazine **305** (66BCJ1988), and from pyrrole **548b** (Scheme 145; 63CPB1431).

Methylation of methylthiotropone **424a** (Scheme 114), according to Seitz and The (87AP362), leads to unstable *sulfonium salt* **425**. This salt can be demethylated and deprotonated (via tropone **426**) to give the resonance-stabilized sulfonium ylide **428**, accompanied by the product **427** of methyl transfer from **425**. Ylide **428** at elevated temperatures undergoes an intermolecular methyl transfer to yield sulfonium salt **424b**.

f. *Reactivity of Fused Benzene Rings.* Examples include the nitration of pyridobenzotropone **207** at the 7-position (89GEP3906920) and the ether cleavage with methoxyfurobenzotropone (76T829). Furthermore, brominated furobenzotropone **429** (Scheme 115) was transformed into thioether **430a** and sulfone **430b** (86JHC257).

## 5. Reactivity at the Heterocyclic Ring

a. *Reactions at Nuclear Nitrogen Atoms.* Azaazulenotropone **262** on *N*-protonation gives tropylium salt **263** (Section II,D,1,b).

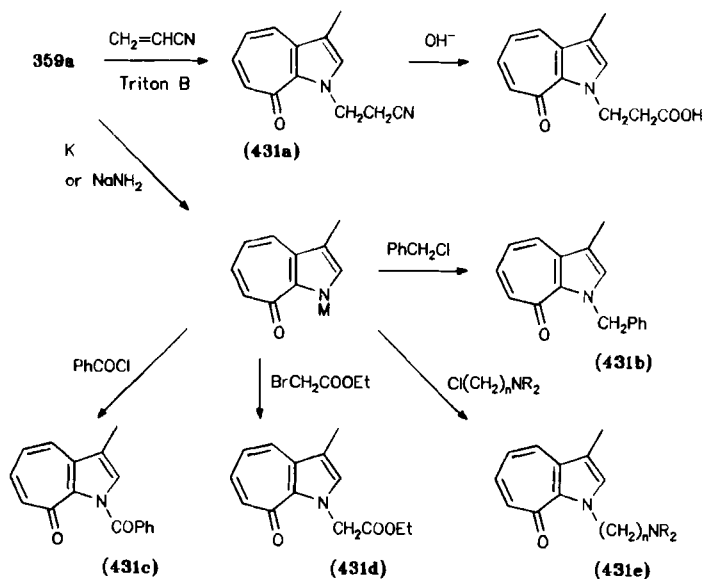


SCHEME 115

*N*-alkylation with pyrrolo- and pyridonotropones and related compounds can be accomplished by alkyl halides and alkali (or methyl iodide and silver oxide), dialkyl sulfates, diazomethane, and so on [64JCS5096; 83USP4381304, 83USP4382088; 84JCS(P1)2297]. Such reactions of tropone **359a** to give derivatives **431a–e** (including cyanethylation and acylation) are shown in Scheme 116 (62YZ408; 65CPB473; cf. 68USP3393208). Triazole **145a** is methylated at the 2-position (64CB1318).

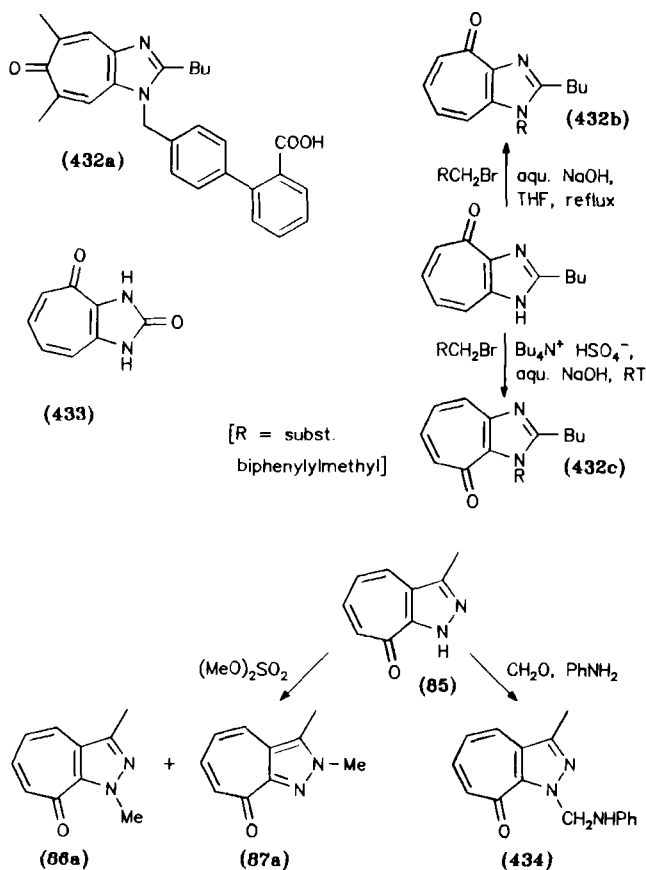
Among imidazotropones, some 4(8)-oxo and 6-oxo compounds exclusively gave a single *N*-alkyl derivative (e.g., 92JHC1219). Further examples include such pharmaceutically interesting 6-oxo products as **432a** (Scheme 117), afforded by means of biphenylmethyl halide, tosylate, or mesylate (91EUP432737, 91MI1). However, 2-alkyl homologs of 4(8)-oxo compound **188** yield, depending on the conditions, a mixture of **432b** and **c** (with sodium carbonate in methanol) or, regioselectively, **432b** or **c** (93GEP4316117, 93MI3; 94MI3).

2-Methylimidazotropone **105a** (69MI1) and tautomerizable 2-oxo derivatives **16** and **433** (65CPB473) give mixtures of 1- and 3-substituted or of mono- and 1,3-disubstituted derivatives. 2-Amino compound **15** is attacked at N-1 or at its oxygen atom (Scheme 110; 62BCJ1188).



[M = Na, K; n = 2 or 3; NR<sub>2</sub> = NMe<sub>2</sub>, NEt<sub>2</sub>, 4-Me-piperazino;  
Triton B = PhCH<sub>2</sub>N<sup>+</sup>Me<sub>3</sub> OH<sup>-</sup>]

SCHEME 116



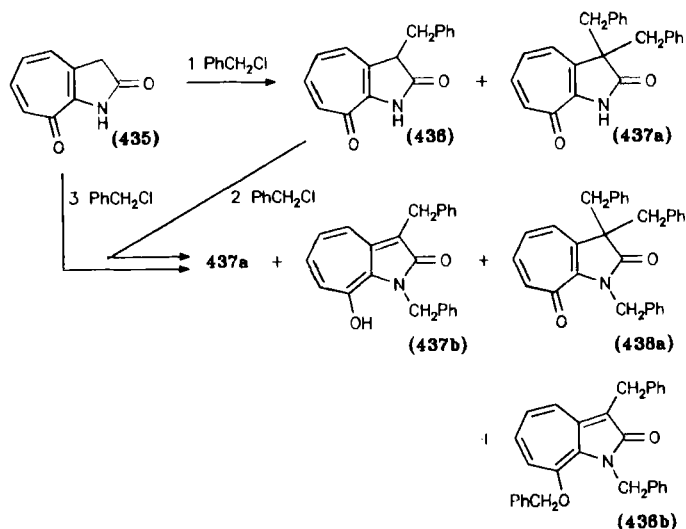
SCHEME 117

Pyrazole **85** undergoes alkylation at N-1 and N-2 (84JHC653; 92CPB1606) and Mannich reaction at N-1 (93JHC1241) to give **86a** and **87a** or **434**, respectively. Likewise, triphenylhexahydrotriazines or bisanilinomethanes can be applied to the aminoalkylation. *N*-Hydroxymethylation of other substrates by formaldehyde/pyridine (68USP3393208) and alkylation by hydroxy and aminoalkyl chlorides (92CPB1606) have also been described.

Finally, during the reactions with one to three molar equivalents of benzyl chloride, pyrrole **435** was attacked at C-3 and at its nitrogen and tropone oxygen atoms (65CPB473); mono- (**436**), di- (**437a,b**), and tribenzyl derivatives (**438a,b**) were isolated (Scheme 118).

*N*-Acylation was accomplished, for example, with indoles **117** and **316** (72BCJ226; 75BCJ314); acyl derivatives are cleaved by alkali or acid





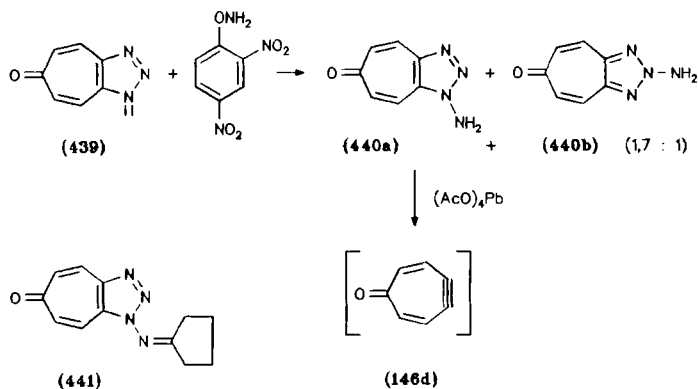
SCHEME 118

[77TL2977; 82IJC(B)765]. Thiazine **361** and oxazines **267** and **297** form acyl derivatives in poor yield or not at all and cannot be alkylated (61BCJ146; 83BCJ2756).

*Quaternization* was reported to fail with pyridotropolones like **503b** (Scheme 133; 54JCS286; 63BCJ1272), probably because of the decreased electron density at the nitrogen atoms in the mesomeric fused tropylium oxide structures. The reaction proceeds smoothly, however, with oxazole **114b** and thiazoles **485a** and **489a** to give quaternary salts **507** and **510a,b** (Scheme 134; 63UP1, 66UP1, and 64UP1, respectively). Surprisingly, oxazolium salt **507** (yellowish-orange) exhibits a distinct maximum in the visible region (Table XIV; 63UP2). In the pyridine series, methiodide **505** (Scheme 133) forms readily (62ZC369).

*N-Amination* of triazolotropone **439** by a hydroxylamine derivative is an important step in the formation and trapping of dehydrotropone (**146d**; Scheme 119). The initial reaction leads to a mixture of the 1- and 2-amino compounds (**440a,b**) that is not separated before the oxidation. The aryne is derived from main product **440a** (e.g., 75AG742; 78TL569). When it is trapped by the morpholine enamine of cyclopentanone, by-product **441** (9%) is observed (86TL3005). The *N*-amino group of ditroponopyrrole **165c** is eliminated by nitric acid to give **165b** (56MI4).

*N-Oxides* are obtained by the reactions of pyridotropones **442** [70BSF3636, 70CR(C)551; 73JHC1075] or pyridotropolone **373** (65MI3) with

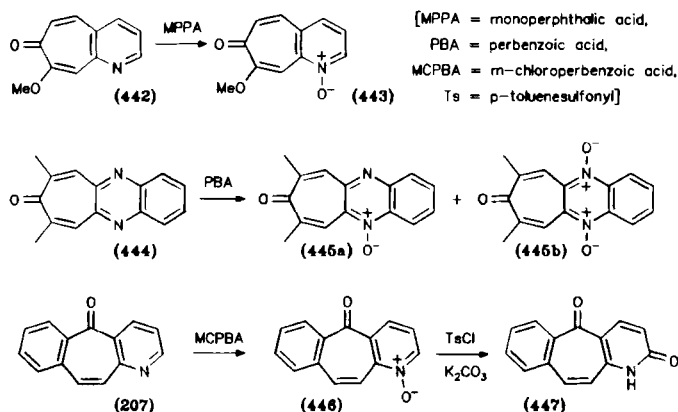


SCHEME 119

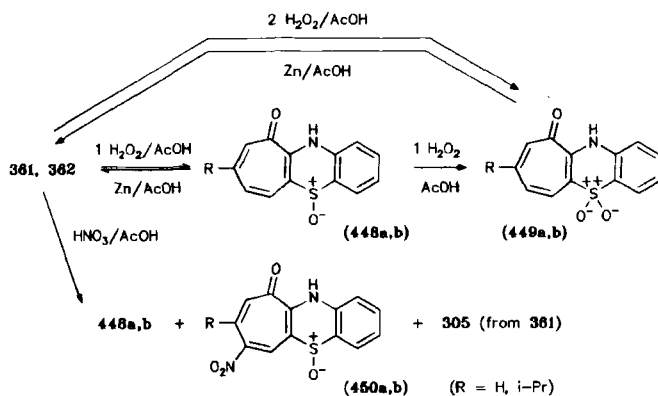
hydrogen peroxide or perbenzoic acids (Scheme 120). Quinoxalotropone **444** gives both mono- and di-*N*-oxides **445a** and **b** (78PJC2045).

In the <sup>1</sup>H-NMR spectra of pyridine oxides (e.g., **443**) a significant low-field shift of H-9 is observed (Table XII). Pyridine oxide **446** shows a transformation, similar to the acetic anhydride rearrangement [84CHEC(2), pp. 224 and 228], to give pyridone **447** (87USP4639457).

*b. Oxidation at Nuclear Sulfur Atoms.* The oxidation of benzothiazinotropones **361** and **362** with hydrogen peroxide (Scheme 121) affords *S*-oxides **448a,b** and *S,S*-dioxides **449a,b** (66BCJ1988). The same tropones, with fuming nitric acid, likewise suffer *S*-oxidation and/or nitration at C-7



SCHEME 120



SCHEME 121

to yield, among other products, nitro-*S*-oxides **450a,b** (66BCJ1980). It is concluded from the experiments described below (Scheme 123) that during the formation of sulfoxides **450** nitration precedes *S*-oxidation (66BCJ1988). Furthermore, tropone **361** and oxides **448a** and **449a** are found among the products following oxidation of 10-methoxybenzotrothiazine with hydrogen peroxide (85BCJ165).

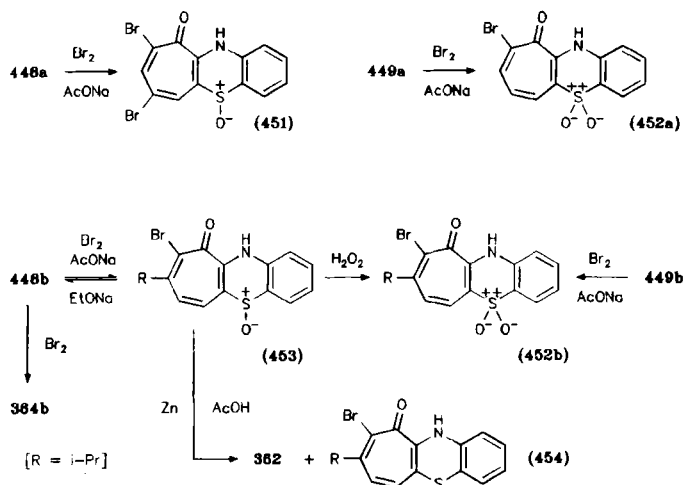
The above-mentioned sulfoxides and sulfones have an acidic character (cf. their UV-spectroscopic behavior, Section III,A,2,c) and are stable to alkali. Unlike sulfones, however, sulfoxides are unstable to acids or to heating and undergo reductive halogenation on treatment with hydrobromic acid (66BCJ1988).

Compared with the parent benzothiazinotropones, these oxides exhibit a greater reactivity toward electrophilic reagents. This is explained by the greater electron density on the rings due to the easier deprotonation of NH. Bromination takes place at C-9 and C-7, and nitration at C-9.

Thus, the bromination of oxides **448** and **449** leads to bromo derivatives **451–454** (Scheme 122). When brominated in the absence of sodium acetate, **448b** yields a small amount of thiazine **364b**. When heated with zinc in acetic acid, sulfoxide **453** is *S*-desoxygenated and partly debrominated to give thiazines **454** and **362**.

On nitrating the same oxides, nitro derivatives **455** and **456** are obtained (Scheme 123). When sulfoxides **455** are treated with zinc in acetic acid, both SO and NO<sub>2</sub> groups are reduced to amino derivatives **457**.

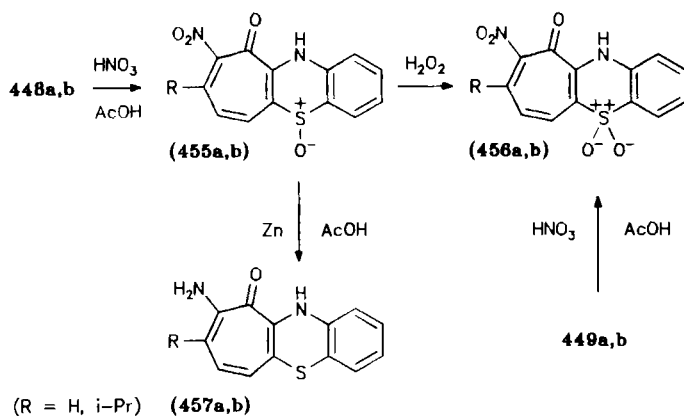
Thienotropones **458a–c**, on oxidation by peracid, yield normal *S,S*-dioxides **459a–c** and thionaphthene *S,S*-dioxides **460a–c** and **462** (Scheme 124; 84BCJ3156). The latter products result from ring contraction (Section



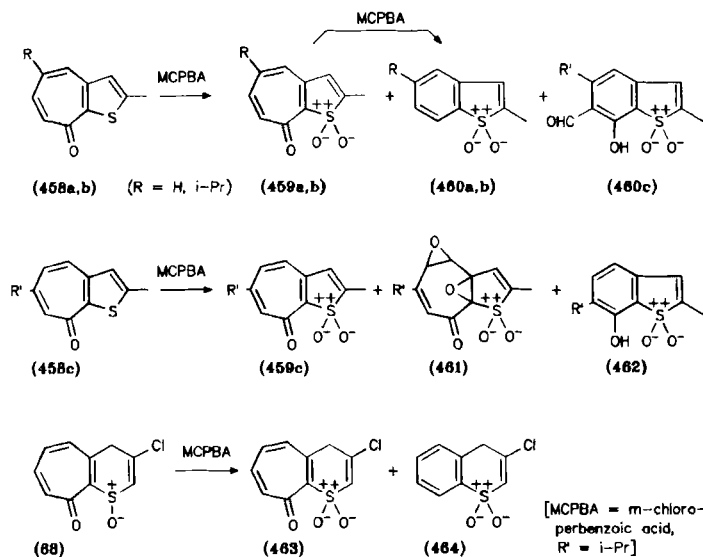
SCHEME 122

IV,A,7,d) of intermediate epoxides (Section IV,A,4,a) such as the (stable) bisepoxide **461**. Similarly, thiopyran *S*-oxide **68** (Scheme 17) gives the corresponding dioxide **463** and its ring-contracted analog **464**.

*c. Electrophilic Reactions at Carbon Ring Atoms.* These reactions are listed in Table XXIV, which permits the following conclusions to be drawn: In the [*b*]-fused systems investigated, the new groups enter the 2- or 3-positions, depending on the vacancy. 2,3-Unsubstituted compounds are



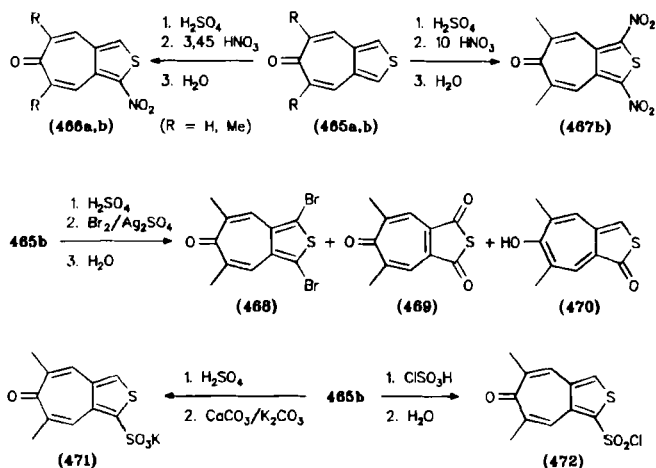
SCHEME 123



SCHEME 124

attacked at C-2, whereas [c]-fused substances give 1- or 1,3-substituted derivatives.

Thus, when nitration, bromination, and sulfonation of thieno[c]tropones **465a** (= **307b**) and **465b** are conducted in the presence of mineral acid, attack occurs at the 1- and 3-positions (Scheme 125; 74YZ1445). For exam-

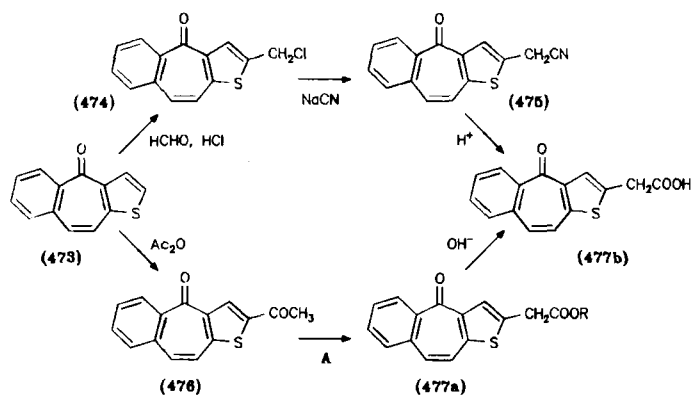


SCHEME 125

TABLE XXIV  
ELECTROPHILIC SUBSTITUTION ON THE HETEROCYCLIC RINGS OF FUSED TROPONIDS

New substituent (position)	Precursor				Scheme	Reagent <sup>a</sup>	New product no.	Reference
	Fused heterocycle	Position of CO	Further groups or rings	Formula no.				
D	(1,3)	[c]furan	6	—	(77)	conc. D <sub>2</sub> SO <sub>4</sub>	—	68T4501
Cl	(2)	[b]pyrrole	8	3-Ph	(76)	NCS	—	77BCJ1184
Br	(2)	[b]furan	8	3-Me	(18)	Br <sub>2</sub>	—	90JHC583
		[b]pyrrole	8	3-Me	96	NBS	<b>359b</b>	61YZ1799
			6	5-OH-3-Ph <sup>c</sup>	98	NBS	<b>368</b>	63CPB1440
						Br <sub>2</sub> <sup>d</sup>	<b>468<sup>e</sup></b>	74YZ1445
SO <sub>3</sub> K	(1,3)	[c]thiophene	6	5,7-di-Me	125	H <sub>2</sub> SO <sub>4</sub> <sup>d</sup>	<b>471</b>	
	(1)	[c]thiophene	6	5,7-di-Me	125	ClSO <sub>3</sub> H <sup>d</sup>	<b>472</b>	
SO <sub>2</sub> Cl	(1)	[c]thiophene	6	5,7-di-Me	125	HNO <sub>3</sub>	— <sup>f</sup>	62BCJ808
NO <sub>2</sub>	(2)	[b]thiophene	6	2-COOH-7-OH-5- <i>i</i> Pr <sup>c</sup>	(99)	HNO <sub>3</sub> <sup>d</sup>	<b>466a,b</b>	74YZ1445
	(1)	[c]thiophene	6	none or 5,7-di-Me	125	HNO <sub>3</sub> <sup>d</sup>	<b>467b</b>	
	(1,3)	[c]thiophene	6	5,7-di-Me	125	HCHO/Me <sub>2</sub> NH	<b>498a</b>	62YZ898
CH <sub>2</sub> NMe <sub>2</sub>	(3)	[b]pyrrole	8	2-Me	132	HCHO/Me <sub>2</sub> NH	<b>498b</b>	62YZ418
				2-Cl	132	HCHO/HCl	<b>474</b>	73GEP2316844
CH <sub>2</sub> Cl	(2)	[b]thiophene <sup>g</sup>	4	5,6-benzo	126 <sup>h</sup>	Ac <sub>2</sub> O	<b>476</b>	
Ac	(2)	[b]thiophene <sup>g</sup>	4	5,6-benzo	126 <sup>h</sup>	GA	—	75GEP2441592
CO(CH <sub>2</sub> ) <sub>3</sub> COOH	(2)	[b]thiophene <sup>g</sup>	4	5,6-benzo	(126)	(AcO) <sub>2</sub> Hg	<b>486a</b>	74YZ1429
Hg(OAc) <sub>2</sub>	(1,3)	[c]thiophene	6	5,7-di-Me	129			

<sup>a</sup> NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, GA = glutaric anhydride. <sup>b</sup> Reagent in excess gives di- and tribromo compounds substituted in both rings (Section IV,A,4,a). <sup>c</sup> Tropolones. <sup>d</sup> For details, see Scheme 125. <sup>e</sup> Besides the products (**469**, **470**) of oxidizing hydrolysis. <sup>f</sup> Decarboxylation; 2,8-dinitro derivative resulting. <sup>g</sup> The numbering used is that of the bicyclic system (e.g., **306**). <sup>h</sup> Following transformations of **474** and **476**, see Section IV,A,5,f.

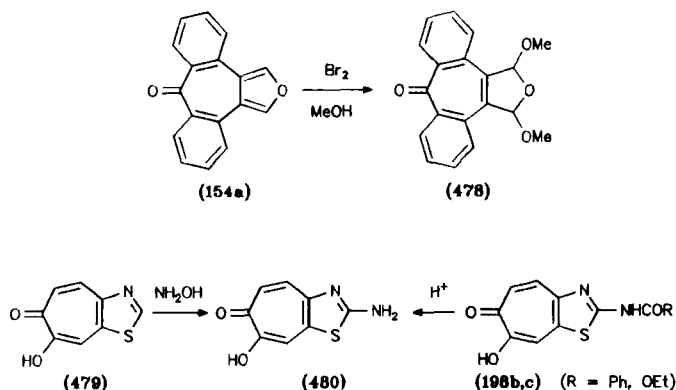


SCHEME 126

ple, nitration of the 1,3-dimethyl analog (**393**) fails. In fact, it is the 6-hydroxythienotropylium ion (whose highest electron densities are at C-1 and C-3) that undergoes these reactions (Sections IV,A,3,b and IV,B,1). The tropone system is later regenerated by hydrolysis.

Deuteration of **307a** exchanges the protons on the furan ring even though protonation by sulfuric acid occurs on the carbonyl oxygen (68T4501, 68TL3771). Since a troponofurion species could not be detected, deuteration is believed to proceed by an electrophilic substitution on the low concentration of the unprotonated form present.

Examples of chloromethylation and Friedel-Crafts reactions (together with side-chain reactions; cf. Section IV,A,5,f) are depicted in Scheme 126.



SCHEME 127

Finally, oxidation by bromine in methanol [84CHEC(4)604] can be applied to tetracyclic furotropone **154a** (Scheme 127); the 1,4-addition of bromine to the diene system yields cyclic diacetal **478** [78ACH(96)393].

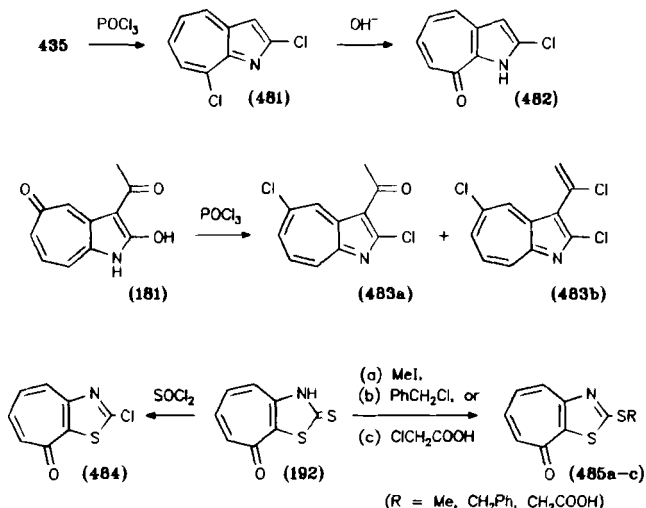
d. *Nucleophilic Reactions at Carbon Ring Atoms.* These reactions are exemplified by the amination [84CHEC(6)259] of thiazolotropolone **479** to give 2-amino compound **480** (for the other synthesis, see Section IV,A,5,e; 62BCJ1998).

e. *Reactivity of Functional Nuclear Substituents.* *Nucleophilic substitution* is illustrated by examples given in Table XXV and Schemes 128–130.

In the furotropone series (71T6023), 2-amino-3-ethoxycarbonyl compound **104a** with alcoholic alkali yields 2-oxo-3-cyano derivative **325b** quantitatively (Scheme 130). A mechanism of ring opening and recyclization passing through the tropolonate-type intermediate **490** is proposed.

Reduction of, or organometallic addition to, 1,3-dibromothienotropone **487a** (74YZ1429) is accompanied by, respectively, complete or partial debromination to afford thienotropylum salt **491**, thienotropylidene **492**, and dimeric thienotropone **494**. The latter may be formed by halogen–metal interconversion (to give **493**) and 1,2-addition of the lithium compound onto the carbonyl group of another molecule **487a**.

*Transformations of individual substituents* include the formation of carboxylic esters and anhydrides (62BCJ808, 62YZ414; 63CPB1431) as well



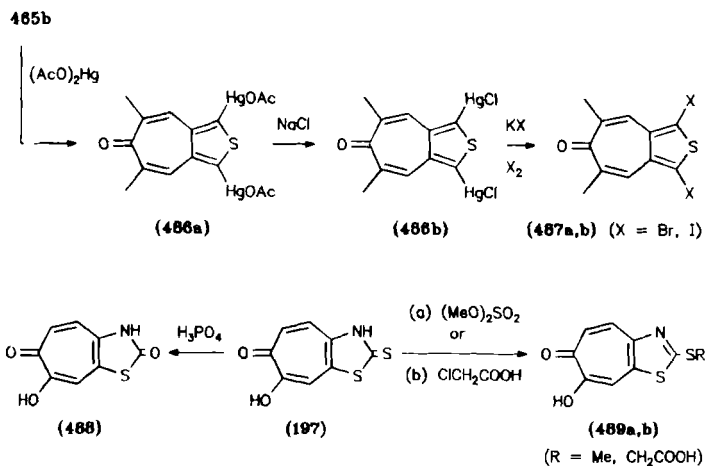
SCHEME 128



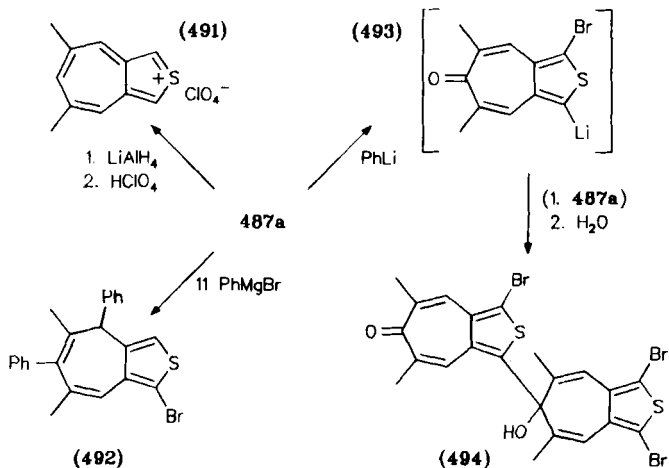
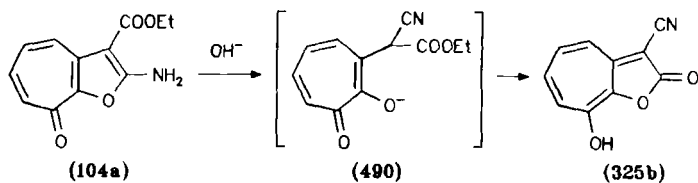
TABLE XXV  
NUCLEOPHILIC EXCHANGE OF SUBSTITUENTS ON THE HETEROCYCLIC RINGS OF FUSED TROPONIDS

New substituent (position) <sup>a</sup>		Precursor					Scheme	Reagent	New product no.	Reference
		Former substituent <sup>a</sup>	Fused heterocycle	Position of CO	Further groups	Formula no.				
Cl	(2)	OH	[b]pyrrole	8	—	<b>435</b>	128	POCl <sub>3</sub>	<b>481<sup>b</sup></b>	62YZ418
				5	3-Ac	<b>181</b>	128	POCl <sub>3</sub>	<b>483a<sup>b</sup></b>	65BCJ306
			imidazole	6	—	<b>16</b>	109	POCl <sub>3</sub>	<b>410b<sup>b</sup></b>	62BCJ1188
			thiazole	8	—	<b>192</b>	128	SOCl <sub>2</sub>	<b>484</b>	64BCJ1526
Br	(2)	Cl	[b]pyrrole	8	—	<b>482</b>	(128)	HBr	—	62YZ418
					3-Me	—	(96)	HBr	<b>359b</b>	61YZ1799
					5,7-di-Me	<b>486b</b>	129	KBr, Br <sub>2</sub>	<b>487a</b>	74YZ1429
					5,7-di-Me	<b>486b</b>	129	KI, I <sub>2</sub>	<b>487b</b>	
I	(1,3)	HgCl	[c]thiophene	6	7-OH <sup>c</sup>	<b>197</b>	129	H <sub>3</sub> PO <sub>4</sub>	<b>488</b>	62BCJ1998
OH	(2)	SH	thiazole	6	7-OH <sup>c</sup>	<b>489b</b>	(129)	HCl	<b>488</b>	
		SCH <sub>2</sub> COOH	thiazole	6	7-OH <sup>c</sup>	<b>489b</b>	(129)	HCl	<b>488</b>	
		NH <sub>2</sub>	[b]furan	8	3-COOEt	<b>104a<sup>d</sup></b>	(25)	H <sub>2</sub> SO <sub>4</sub>	<b>325a</b>	71T6023
		NMe <sub>2</sub>	[b]pyrrole	8	3-CN	<b>129<sup>d</sup></b>	(30)	HBr	<b>435</b>	62YZ418
		Cl	[b]furan	8	3-CN	—	(83)	NaOH	<b>325b</b>	71T6023
NH <sub>2</sub>	(2)	Cl	thiazole	8	—	<b>484</b>	(128)	NH <sub>3</sub>	—	64BCJ1526

<sup>a</sup> OH, SH, or tautomers, oxo, thioxo, respectively. <sup>b</sup> Tropone and acetyl carbonyl groups of **435**, **181**, and **16** are likewise chlorinated. <sup>c</sup> Tropolone. <sup>d</sup> Hydrolysis and decarboxylation.



SCHEME 129



SCHEME 130

as the hydrolysis of esters [52CI(L)471; 63CPB1440] and nitriles (62YZ418; 71T6023). Decarboxylation proceeds in the presence of copper/quinoline (63CPB1431) or trifluoroacetic acid (84USP4440779). The 3-carbamoyl derivative of pyrrolone **435** is hydrolyzed and decarboxylated by hydrobromic acid (62YZ418).

Thiazolotropolone amide **200** is dehydrated to yield the corresponding nitrile **495** (Scheme 131). The subsequent reaction with cysteine gives a seven-membered-ring analog (**496**) of firefly luciferin (63BCJ173).

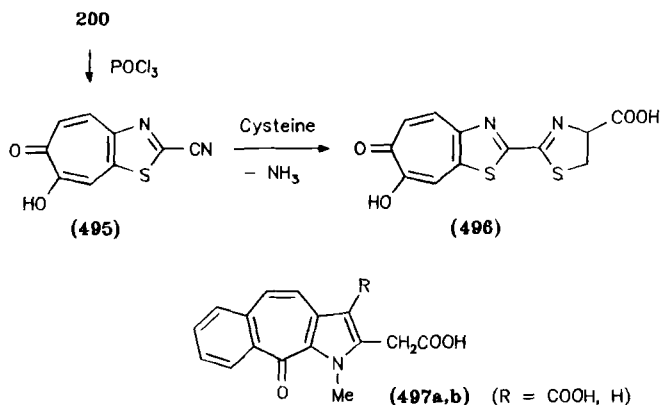
For transformations of amino groups, refer to alkylation and acylation (71T6023) or desacylation (Scheme 127; 62BCJ1998).

Starting from 2-mercaptothiazoles **192** and **197**, alkylation leads to the respective thioethers **485a–c** (Scheme 128) and **489a,b** (Scheme 129), whereas oxidation by hydrogen peroxide gives the disulfides and/or the parent compounds (e.g., **479**; 64BCJ1526 and 62BCJ1998, respectively).

The synthesis of cyanine dyes **512a,b** from (quaternized) 2-methylthiothiazolotroponeoids **485a** and **489a** is shown, together with another type of formation, in Scheme 134 (64UP1; 66UP1). The electronic spectrum of dye **512b**, compared with that of the symmetrical thiomonomethine cyanine ( $\lambda_{\max}$  427 nm), exhibits a bathochromic shift up to 484 nm.

f. *Reactivity of Side Chains and Fused Carbocyclic Rings.* Transformations on functionalized side chains of thienobenzotropone **473** (Scheme 126; 73GEP2316844; 74GEP2346747) include the following examples:

1. substitution (to give **475**) or reductive dehalogenation of chloromethyl compound **474**;
2. oxidation/esterification of acetyl derivative **476**;
3. hydrolysis of nitrile **475** or ester **477a**.



SCHEME 131

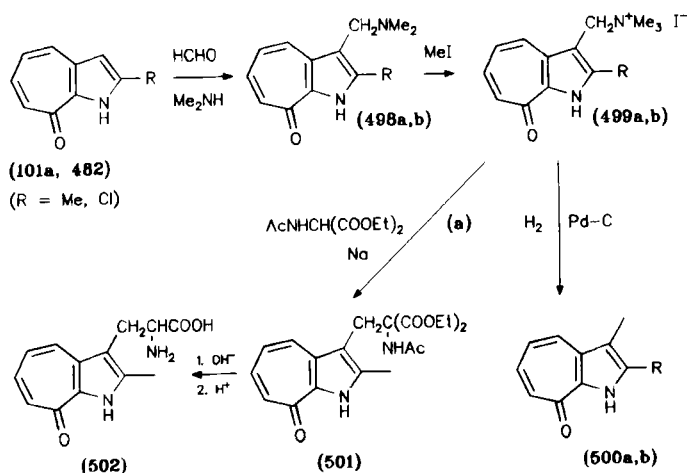
Pyrrole derivatives like monocarboxylic acid **497b** are made by selectively esterifying the carboxymethyl group of diacid **497a**, followed by decarboxylation and hydrolysis (81EUP24807).

The Mannich bases (Table XXIV) obtained from pyrrolotropones **101a** and **482** (Scheme 132) can be quaternized and subsequently hydrogenated to give 3-methyl derivatives **500a,b** (62YZ418, 62YZ898). However, quaternary salt **499a**, on condensation with acetaminomalonic ester, offers a convenient route to the seven-membered-ring analog (**502**) of tryptophan.

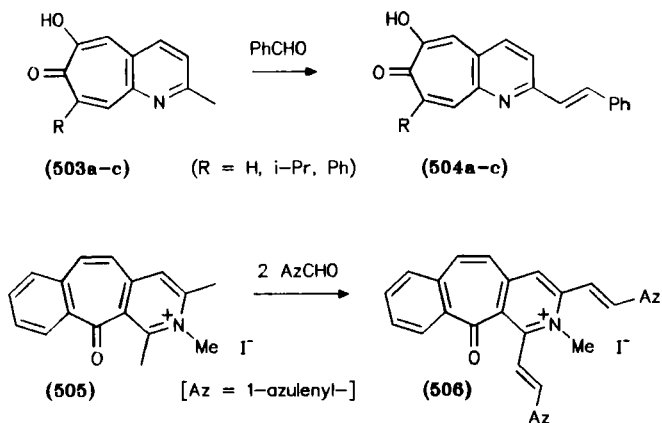
On deprotonation, methyl groups at carbon atoms adjacent to a nitrogen atom often have sufficient acidity to provide the anionic character necessary to effect condensation with aromatic aldehydes or cyanine-dye-forming synthons. Thus, 2-methylpyridotropolones **503a-c** (Scheme 133) give styryl derivatives **504a-c** (63BCJ1272; 65MI3; 68NKZ620).

The reactivity of these methyl groups is normally enhanced by nitrogen atom quaternization. Benzotroponopyridinium salt **505** with two molecules of azulene aldehyde condenses to afford blue-black bis(azulenylvinyl) dye **506** ( $\lambda_{\max}$  536 nm; 62ZC369). Furthermore, oxazolium salt **507** condenses with activated benzothiazolium salt **508** (Scheme 134) to form unsymmetrical trimethine cyanine **509** (63UP1). (Dyes **512a,b** arise from methylthio exchange; Section IV,A,5,e.)

The cycloaliphatic rings of pyrrolotropone **316** (75BCJ314) and of the analogous furan (82BCJ3242) are dehydrogenated by DDQ or chloranil or in the presence of palladium-charcoal to yield indolo- and benzofurotropones.



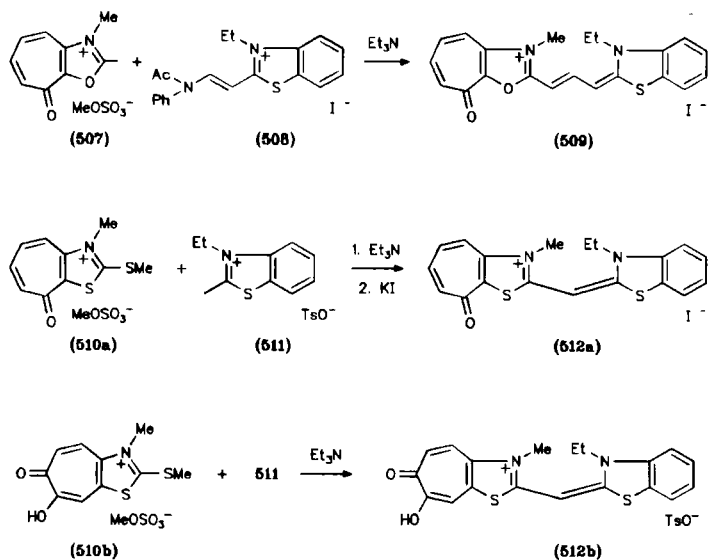
SCHEME 132



SCHEME 133

## 6. Cyclization Reactions

a. *Cyclocondensations.* Cyclocondensations onto the seven-membered ring are illustrated by the reactions of pyridotropolones **503a-c** (63BCJ1272;

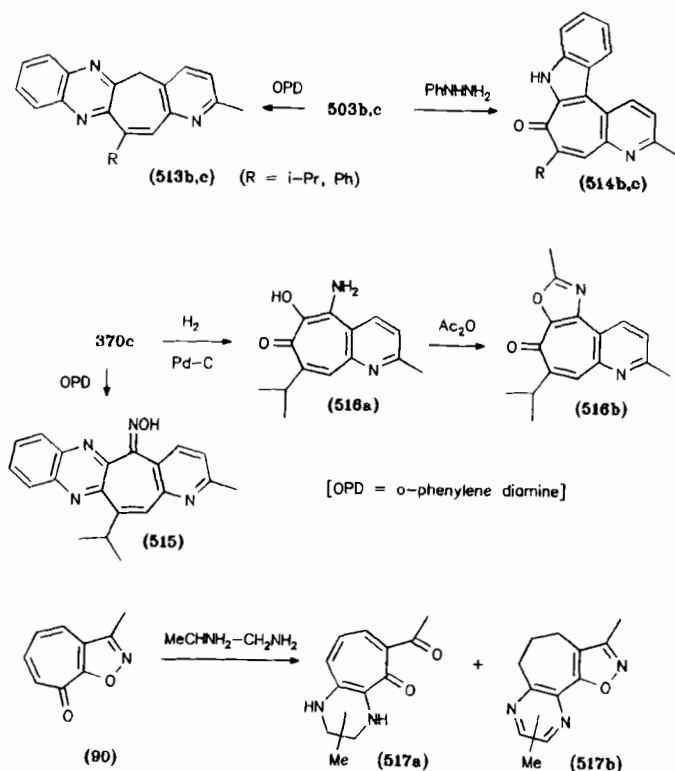


SCHEME 134

65M13; 68NKZ620). Apparently existing in the tautomeric 1,2-diketone structures (like **389**), they condense with *o*-phenylene diamine (OPD) **138** to give quinoxaline system **513** (Scheme 135). This system occurs, according to its reactivity and spectra, as a methylene tautomer rather than as an NH-containing species.

Precursors **503b** and **c**, which are substituted in the 8-position, undergo Fischer's indole synthesis leading to tetracyclic tropones **514b,c**. 5-Nitroso derivative **370c** (derived from **503b**) gives quinoxalotroponeoxime **515** and, via amine **516a**, oxazolotropone **516b** (59NKZ1175).

Reactions of isoxazolo[5,4-d]pyridine **90** with 1,2-diaminoethane or -propane afford, for instance, mixtures of isomeric dihydropyrazines **517a** and isomeric pyrazines **517b** in low yields [83H(20)1117]. The latter structure is the result of double-bond migration from the seven-membered ring into the heterocyclic one.



SCHEME 135

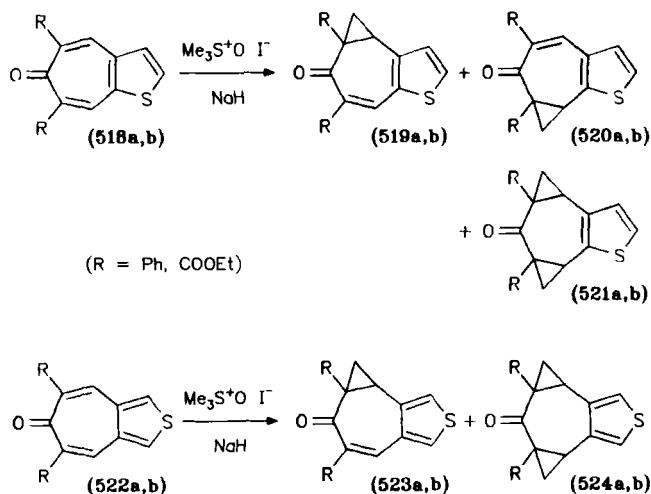
b. *Cycloadditions*.<sup>4</sup> Many troponoids readily react with sulfur ylides, dienophiles, and other partners to yield cyclic adducts [71PAC239, p. 250; 73CRV293, p. 356; 76MI1; 85HOU(5/2c)710, p. 755].

Sulfur ylides (like the Corey reagent, dimethylsulfoxonium methylide) or dihalocarbene precursors (e.g., haloform/sodium hydroxide) are capable of adding (dihalo)methylene groups to one or two tropone double bonds of thienotropones; these reactions give homo- or bishomotropones [74CR(C)295; 77BSF(2)571; 85JCS(P1)983; 86CJC1360].

Thus, on treating thienotropones **518a,b** and **522a,b** with the sulfur ylide (Scheme 136), all possible adducts in the [b]- and [c]-series (**519–521** and **523–524**, respectively) were isolated. The reactivities depend on the solvent and on the substitution of the tropone rings; parent or methyl compounds are less reactive. The structures of the adducts were established by comparison with deuterated analogs.

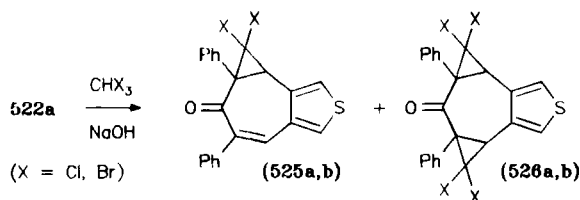
Attack by dihalocarbenes on diphenyltropone **522a** (Scheme 137) leads to mono- and bis-cyclopropanation [**525, 526**; 77BSF(2)571]. With dichlorocarbene, bis(carbethoxy) (**522b**) and dimethyl derivatives give mono- or bishomotropones, respectively.

Addition of dienophiles preferentially occurs onto the heterocyclic rings of tropones [c]-fused onto furan and pyrrole [cf. 84CHEC(4)67]. Furotropone **307a** and dimethyl acetylene dicarboxylate (DMAD) give a dimerized adduct that undergoes cycloreversion at higher temperature to form monomeric adduct **527** (Scheme 138; 91CB2465). The 5,7-bis(carbomethoxy)



SCHEME 136

<sup>4</sup> Without regard to the stereochemistry.



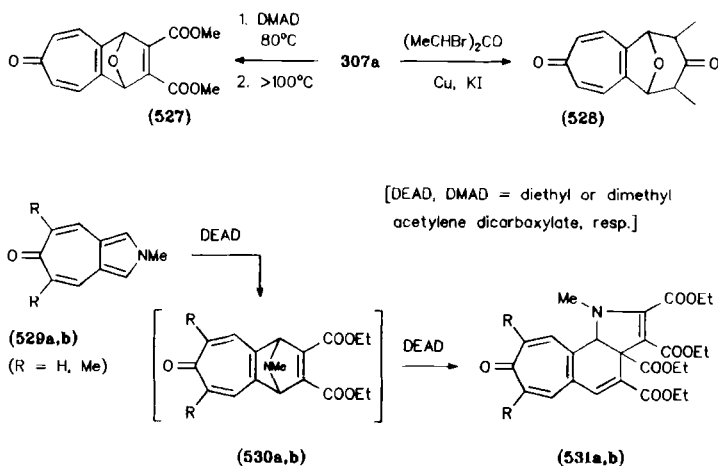
SCHEME 137

derivative of **307a** with diethyl acetylene dicarboxylate (DEAD) directly yields the corresponding adduct. (Regarding the formation of **528**, see the last paragraph of this section.)

However, tropone **307a** does not add tetracyanoethylene (68T4501), nor do thienotropones **315a,b** add maleic anhydride (67JOC1610). Similarly, oxepinotropone **374** does not react with dienophiles [94H(38)957].

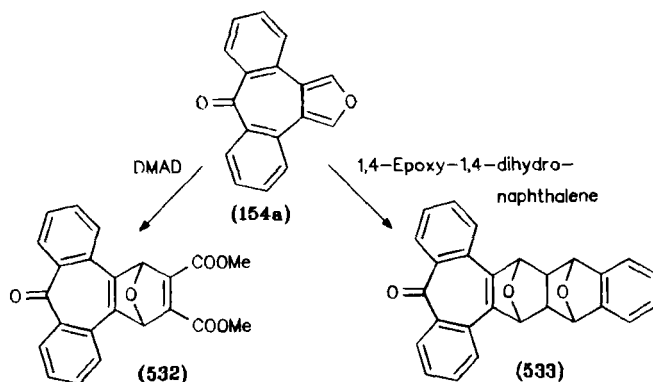
Among the pyrrolo[c]tropones, derivatives **529a,b** add DEAD (as an electron-deficient dienophile of relatively low LUMO energy level) and yield the final 1:2 adducts **531a,b** (85T3303). Kinetic studies made by NMR spectroscopy show that the reactions pass through 1:1 adducts **530a,b** and primary 1:2 adducts; the latter can be isolated in the case of **529a**. It has been reported, however, that **264**-type pyrrolotropones do not react with DEAD (75AG840).

Dibenzofurotropones **154**, which originate from cycloadducts (Section II,A,3,i), add a number of ethylenic dienophiles more readily than bicyclic



SCHEME 138





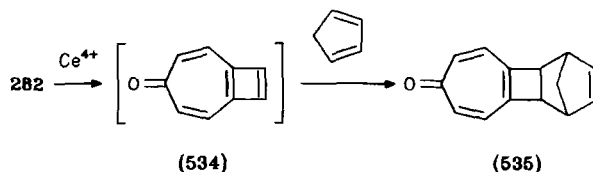
SCHEME 139

**307a** does (68CB3122; 76JOC1425). They react not only with electron-deficient synthons like DMAD (to give **532**, Scheme 139), tetracyanoethylene, *p*-benzoquinone, *N*-phenylmaleimide, ethyl acrylate, and maleic anhydride, but also, exceptionally, with the electron-rich and strained olefin 1,4-epoxy-1,4-dihydronaphthalene (to give **533**). The controlling factors in reactivity and stereospecificity of these cycloadditions were extensively investigated (76T2879).

Oxidation of cyclobutadienotropone iron complex **282** generates the free ligand **534** (Scheme 140), which can be trapped as an adduct (**535**) with cyclopentadiene (78AJC1607).

Other related reactions with the heterocyclic or seven-membered rings consist in

1. formation of adduct **528** (Scheme 138) by [3+4]-cycloaddition of an allyl cation [85CHEC(1)418], formed by reductive dehalogenation of dibromopentanone (79CL43);
2. closure of an additional furan ring by Claisen rearrangement of pyridonotropolone propargyl ethers (USP4130649);
3. nucleophilic additions onto quinoxalotropones like **376** (Section IV,A,4,b);



SCHEME 140

4. addition of hydrazine onto pyridobenzotropones like **391** (Section IV,A,4,c); and
5. attack of cyclopropenes onto triazinotropone **542** (Section IV,A,7,c).

## 7. Ring Cleavage and Transformation

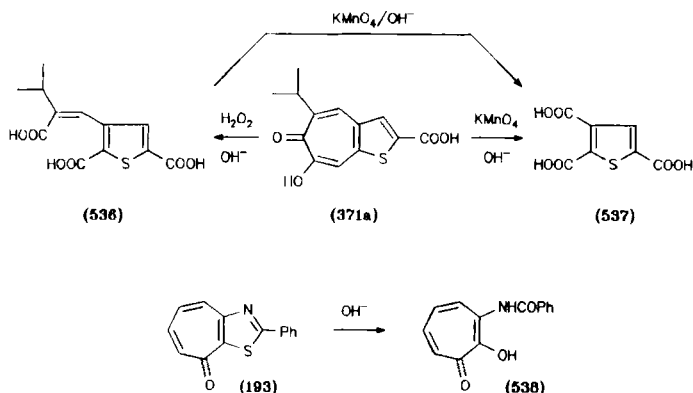
a. *Oxidative Degradation of the Seven-Membered Ring.* With benzotropolones, under mild or drastic conditions, oxidative degradation of the seven-membered ring leads to derivatives of *o*-carboxycinnamic acid (by alkaline hydrogen peroxide) or of phthalic acid (by alkaline potassium permanganate), respectively (59MI1, p. 390). Consequently, the degradation of thienotropolone **371a** (Scheme 141) or of thiazolotropolone **198b** can afford **536**- or **537**-type carboxylic acids (62BCJ808, 62BCJ1998).

The heterocyclic dicarboxylic acids obtained by exhaustive oxidation formerly served for structure elucidation. Thus, derivatives of the following acids were isolated:

1. pyrazole-3,4-dicarboxylic acid from **81a,b** and **142** (66BCJ253), **83** (65BCJ362), and **98a** and **388** (58MI1);
2. thiazole-4,5-dicarboxylic acid from **191** (64BCJ1526);
3. quinolinic acid from **209** [52CI(L)562]; and
4. quinoxaline 2,3-dicarboxylic acid from **27** (58MI2).

The oxidation of dibenzo derivative **322** cleaves both nonbenzenoidic rings and gives phthalic acid [78IJC(B)567].

b. *Cleavage of the Heterocyclic Ring.* Such cleavage commonly occurs on alkaline or acidic hydrolysis and often proves to be the reverse synthesis. Thus, the following compounds are obtained under basic conditions:



SCHEME 141

1. 3-acetyltyropolone **99** (cf. Scheme 24) from furotropone **100** [65-BCJ301; 73JCS(P1)1960];
2. bitropolonyls (e.g., **163**; cf. Scheme 39) from furo- and pyrrolobitropones like **164** and **165b** (56MI4; 67TL423);
3. 3-aminotyropolone **112** (cf. Scheme 27) from oxazolotropones **114a,b** with alkali (or acid) or liquid ammonia (61BCJ312);
4. 2-benzoylamino-5-hydroxytropone from oxazolotropone **24a** (67CPB-619); and
5. 3-benzoylamino-5-hydroxytropone **538** (Scheme 141) from thiazolotropone **193** (64BCJ1526).

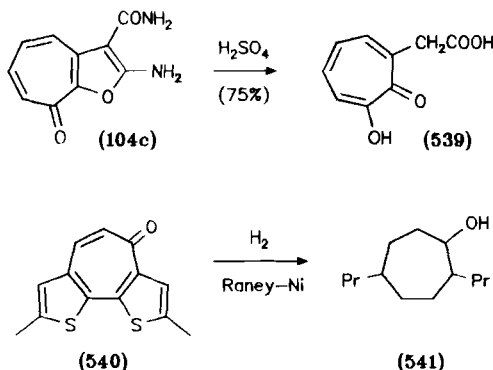
When heated in sulfuric acid, furotropone **104c** (Scheme 142; 71T6023) gives tyropolone-3-acetic acid **539**. 2-Alkylamino-3-acetyltyropolones are by-products of the furotropone to pyrrolotropone transformation (cf. Scheme 37) if bulky alkyl groups are present (80BCJ3373).

Triazolotropone **440a** expels the heteroring on oxidation (Scheme 119; 75AG742); and from dithienotropone **540**, after exhaustive hydrogenation, cycloheptanol **541** remains [92IJC(B)449].

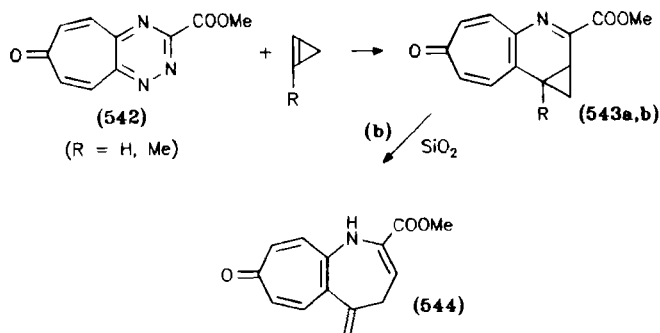
c. *Exchange of the Heterocyclic Ring.* This reaction was discussed in the synthetic Section II,A,3,j. Further examples include transformations of furoditropone **164** (Section II,A,3,k) and furotropone **631** [Scheme 170; 93H(36)1725].

Reactions of triazinotropone **542** (Scheme 143) with cyclopropenes gave norcaradiene derivatives **543a,b** that did not rearrange to the tautomeric 1-azaheptalene system, but rather gave azepine **544** (83LA1845).

d. *Ring Contraction.* Ring contraction of troponoids to benzene derivatives often occurs simultaneously and competitively with nucleophilic dis-



SCHEME 142



SCHEME 143

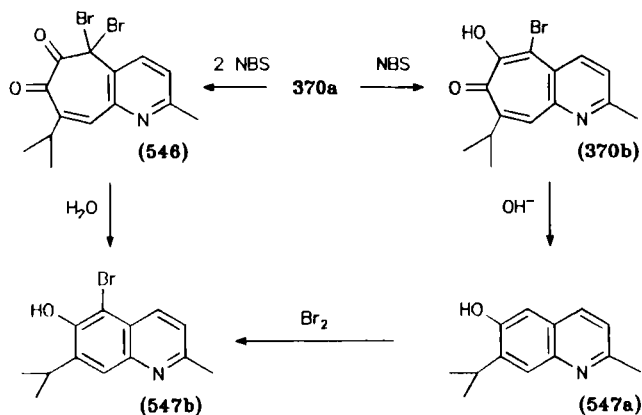
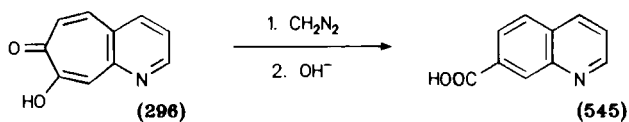
placement of a substituent, the proportions of the two reactions varying considerably. The rearrangements can serve in structural clarification. They are typical of basic conditions and are preferentially given by substrates carrying a good leaving group (55CRV9, p. 75; 66MI2, pp. 138 and 146; 73CRV293, p. 352; 74MI1).

In the case of 2-halotropones, for instance, the reaction is believed to begin with the attack of hydroxide ion onto C-1 or C-3, and it results in the formation of benzoic acid or salicylaldehyde, respectively. The balance between the two processes is affected by the alkali concentration: More dilute alkali favors the second route. According to Pietra (79ACR132), the key step of the first route is ring closure in the initial hydroxide adduct to give a norcaradiene intermediate.

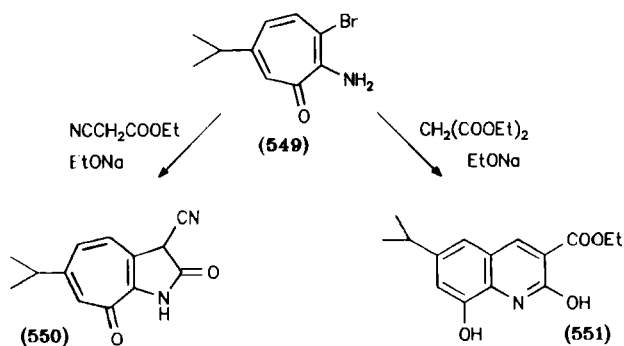
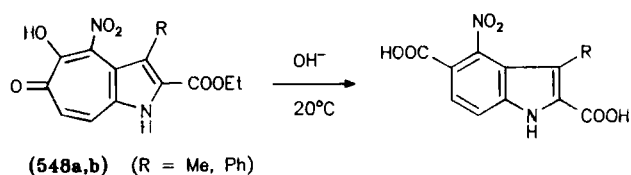
The transformations of tropolones to give benzoic acids are analogously interpreted; they resemble benzilic acid rearrangements. Examples from the heterocyclotropolone series are shown in the Schemes 144 and 145. Pyridotropolones **296** (59MI4) and **370a** (61BCJ42; 67BCJ680), under the influence of certain reagents, give carboxy- or hydroxyquinolines (**545**; **547a,b**), respectively. Monobromotropolone **370b** rearranges, like **546**, via its tautomeric dicarbonyl structure.

With nitropyrrolotropolones **548a,b** (Scheme 145), ring contraction accompanying ester hydrolysis takes the same course (63CPB1431). (The introduction of nitro groups into tropolones favors the rearrangement.) The corresponding bromo derivative **366b** is smoothly hydrolyzed to carboxylic acid **366a** *without* ring contraction (63CPB1440). Furthermore, indolotropolone **301** is not changed, even by fusion with alkali [70JPR(312)466].

In this connection, the limitations of the pyrrole ring annulation onto 2-amino-3-bromotropones were investigated (63MI2). With **549**, the frontier between the "normal" cyclization (to type **550**) and the rearrangement (to give 8-hydroxyquinoline **551**) lies between the uses of cyanoacetate and



SCHEME 144

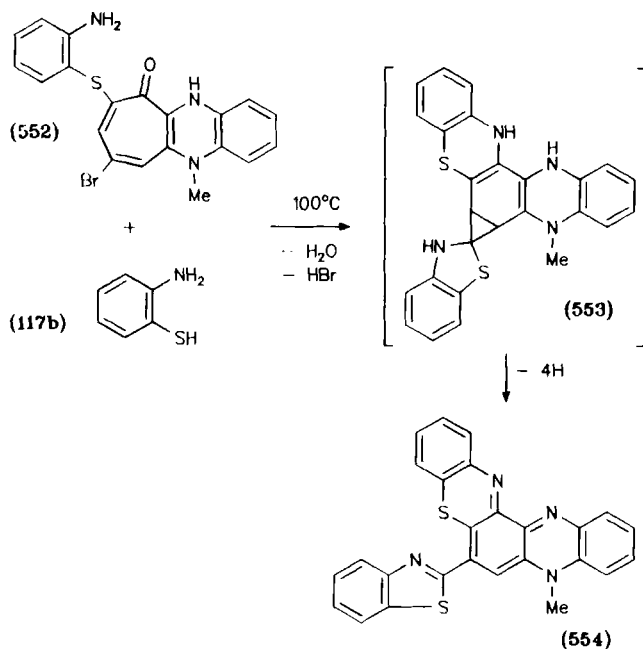


SCHEME 145

malonate. Many other reactions, if occurring at all, lead to analogous quinolines.

Another example of bromotropone contraction is derived from Nozoe's benzotropazine chemistry [Scheme 146; 89H(29)1459]. Condensation of tropone **552** with further *o*-aminothiophenol (**117b**) gave benzenoid compound **554** instead of the expected tris(benzazino)tropyliene. Presumably, this condensation takes place via initial cyclization (to benzothiazine), then cyclocondensation (to spirobenzothiazoline), followed by tautomerization (to norcaradiene **553**), ring contraction, and dehydrogenation.

The formation of thienotropone dioxides was accompanied by ring contraction (Section IV,A,5,b; Scheme 124; 84BCJ3156) to give thieno-fused derivatives of benzene (**460a,b**), phenol (**462**), and salicylaldehyde (**460c**). Among the specific features of this rearrangement are a large influence of the substituents on the site of the reaction, the formation of aromatic compounds at a different oxidation level, and the presumed existence of two different mechanisms (oxidative decarbonylation and hydrolytic contraction of the epoxides).



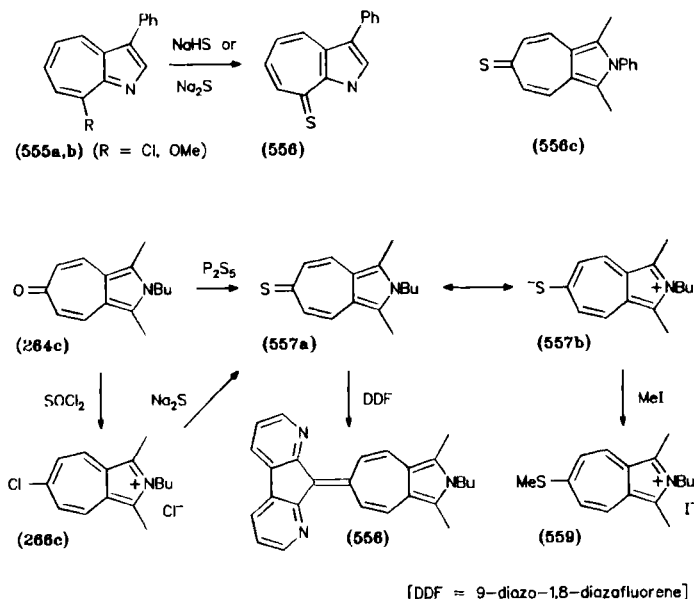
SCHEME 146

## 8. Sulfur and Nitrogen Analogs of Tropones

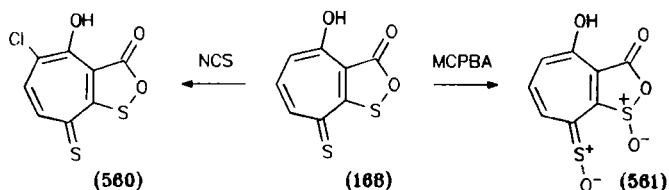
a. *Tropothiones*. Pyrrolotropothione derivatives like **556** (Scheme 147) can be easily prepared from azaazulenes (**555a,b**) carrying a displaceable substituent with sodium (hydrogen) sulfide (67CPB634; 77BCJ1184). Indolotropothione is similarly obtained (76BCJ1101). Other routes lead from tropones (**264c**, **315c**), directly or via chlorotropylum salts (**266c**), to tropothiones **557** or **556c**, respectively (79CB2087; 91KGS1432).

In no case could tautomeric mercaptoazaazulenes be detected. The thiones are relatively stable, comparable with the dibenzo derivative, unlike the parent tropothione (73CRV293, p. 306). In the electronic spectra, the change from tropone to tropothione is connected with a bathochromic shift (67CPB634; 79CB2087). The participation of a dipolar resonance structure **557b** is expressed by the large dipole moment (Table XVIII) and by significant low-field shifts, compared to tropone **264c**, in the  $^{13}\text{C}$ -NMR spectrum. Likewise, the  $^1\text{H}$ -NMR spectrum of thione **556c** (91KGS1432), in relation to tropone **315c** (69ZOR570), shows low-field shifts.

Tropothione **557** can be *S*-alkylated to give tropylium salt **559** or condensed (by the diazo method) to give heptafulvene **558** [79CB2087; 91KGS1432; cf. 85HOU(5/2c)710, p. 766. and Section IV.A,4,c]. Reactions of the natural antibiotic thiotropocin **168** (Schemes 73 and 148) afford



SCHEME 147



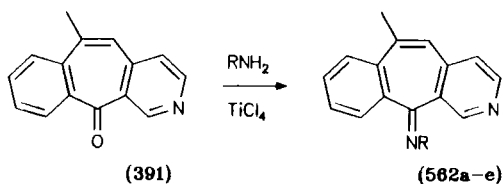
SCHEME 148

thioethers (**294b** and the *S*-methyl derivative), chloride **560**, and *S,S'*-dioxide **561** (84TL419; 92JA8479).

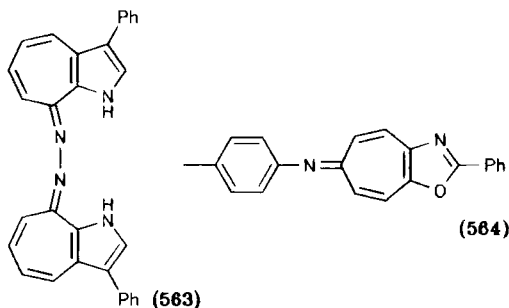
b. *Troponeimines*. Regarding troponeimines, typical “carbonyl derivatives” and their *formation* from tropones have already been mentioned (Sections IV,A,1 and IV,A,4,c). In the monocyclic series, *N*-unsubstituted or *N*-alkylated derivatives are extremely unstable [73CRV293, p. 307; 85HOU(5/2c)710, p. 745]. Among fused analogs like **562a–e** (Scheme 149), prepared in the presence of titanium tetrachloride, even imine **562a** is unusually stable (82JHC897, 82JHC967; 85JHC555, 85JHC805).

Furthermore, the following substrates can be iminated:

1. dichloro-1,3-diazaazulene **410b** at the 6-position by ammonia (62BCJ1188);



(R = H, Me, CH<sub>2</sub>CH=CH<sub>2</sub>, CH<sub>2</sub>Ph, CH<sub>2</sub>CH<sub>2</sub>NMe<sub>2</sub>)



SCHEME 149



2. chloro- and methoxy-1-azaazulenes **555a,b** by ammonia (77BCJ1184), methylamine (67CPB634), or hydrazine (54MI2), the latter reagent giving both hydrazone and azine **563**;

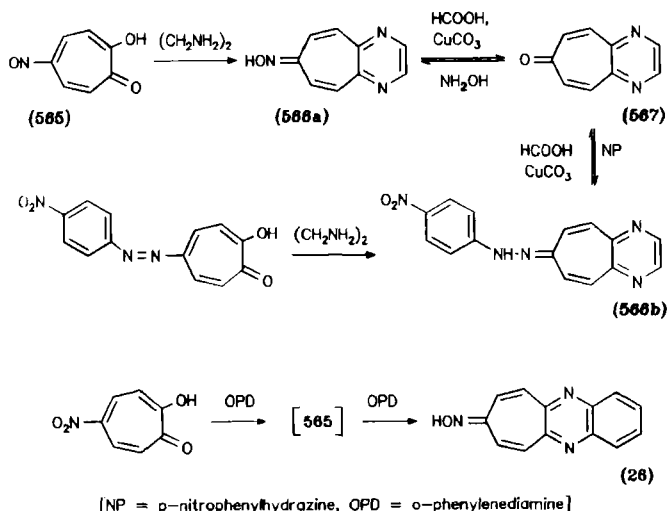
3. chlorobenzo-1-azaazulene by hydrazine (75BCJ314);

4. methylamino-1,2-diazaazulene by hydrazine under amine exchange (84JHC653); and

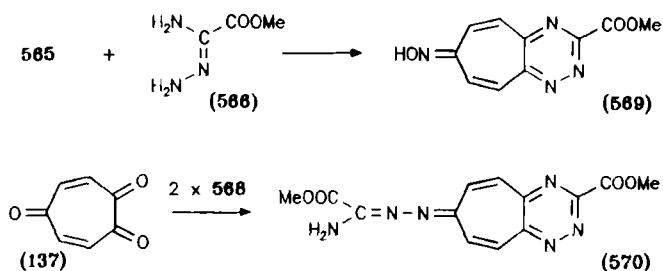
5. oxazolo- or imidazotropones **24a,c** by *p*-toluidine to give aniles, for example, **564** (67CPB627).

Other imino derivatives arise, as by-products or in side reactions, on heterocyclization. Thus, the treatment of cinnamoyltropolones **75** with hydroxylamine (Scheme 19) yields, in the case of the 5-nitro derivative, the corresponding isoxazolotroponeoxime (89JHC371). The formation of oximes and several hydrazones from 3-acetyltropolone or its derivatives has also been mentioned (Section II,A,3,c). Moreover, an azine was obtained in addition to quinoxalotropone **213** (Section II,B,2,c); a tropone immonium salt was isolated after an extremely complex diene reaction of an 6-amino-2-azaazulene (93CB441).

Fused tropone oximes and arylhydrazones are formed on cyclizing 5-nitroso- or 5-arylazotropolones with bifunctional synthons (cf. Sections II,A,1,d and II,A,3,g). Among numerous further examples [e.g., 53MI2; 57DOK(115)526; 59NKZ1175], some reactions show specific features (Schemes 150–152).



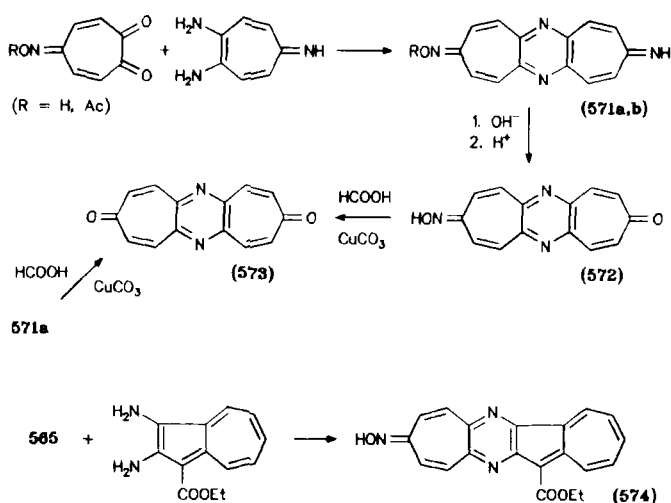
SCHEME 150



SCHEME 151

Thus, cyclocondensation by ethylenediamine to give pyrazines like **566a,b** includes spontaneous dehydrogenation (58MI3; 63CPB1423). In the reaction forming quinoxaline **26** (59MI5), 5-nitrotropolone **565** can be replaced by tropoquinone di- and trioximes and even by 5-nitrotropolone, which is presumably first reduced by *o*-phenylenediamine. Nitrotropolones bearing sterically hindering substituents give rise to lower yields and side reactions.

The use of one or two molar equivalents of amidrazone **568** leads to the formation of [1,2,4]triazinotroponeoxime **569** or hydrazone **570**, respectively (Scheme 151; 83LA1845). Finally, Scheme 152 shows the syntheses of several interesting compounds, including pyrazinoditropone **573** and its oximes **571** and **572** (61BCJ151) as well as azulenopyrazinotroponeoxime **574** (73BCJ3161).



SCHEME 152

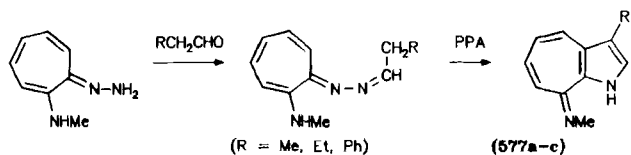
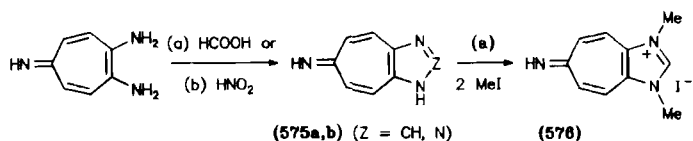
Cyclizations to give imidazo- and triazolotroponeimines **575a,b** (Scheme 153) start from 4,5-diaminotroponeimine (53MI1; 54MI1). A route leading to pyrrolotroponeimines like **577** is an analog of the Fischer indolization (67CPB634).

Investigations on *tautomerism* in most cases proved the predominant or exclusive existence of imino rather than amino forms. These conclusions were derived from electronic and other spectra, quantum chemical calculations (MNDO; 92JHC1219), and reactivities. Thus, imidazotroponeimine **575a** lacks amine reactions (53MI1); its 2-amino derivative **14c** is diazotized at the 2-position (62BCJ1188).

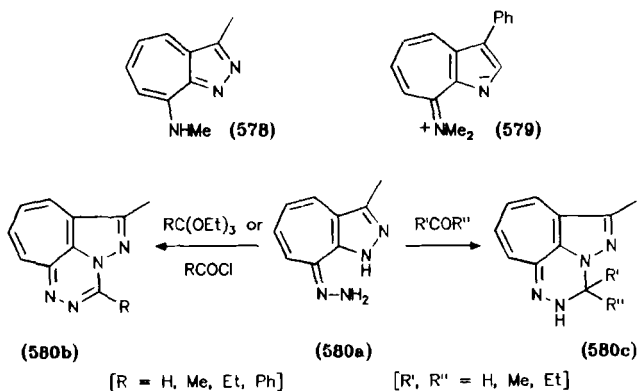
By contrast, Kon (54MI3) deduced from LCAO MO calculations that these "anomalous amine properties" are not due to tautomerism and that aminodiazaazulenes indeed exist. In any case, pyrazole **578** (Scheme 154) seems to have the amine structure [83H(20)9]. As regards dimethylaminoazaazulenes, the contribution of mesomeric zwitterionic forms like **579** is assumed (68BCJ2102; 77BCJ1184).

The *electronic spectra* of parent troponeimine (73CRV293, p. 332) and of many fused derivatives (like **577a**) are similar to those of the corresponding tropones, but bathochromically shifted (67CPB634; 77BCJ1184). In addition, bathochromic shifts can occur in alkaline solution (58MI2, 58MI3; 62BCJ1188) or even in acid solution (56MI3). In the spectra of oximes **571** and **572** the characteristic fine structure known from parent ditropone **573** is missing (61BCJ151).

Fused troponeimines show a number of tropone *reactions*, such as hydrogenation to give fused amino- or acetamidocycloheptenes (53MI1; 54MI1; 58MI2), oxidative ring degradation (53MI1; 58MI2, 58MI3; 61BCJ151; 73BCJ3161), or alkylation and quaternization to give imidazolium salt **576** (53MI1).



SCHEME 153

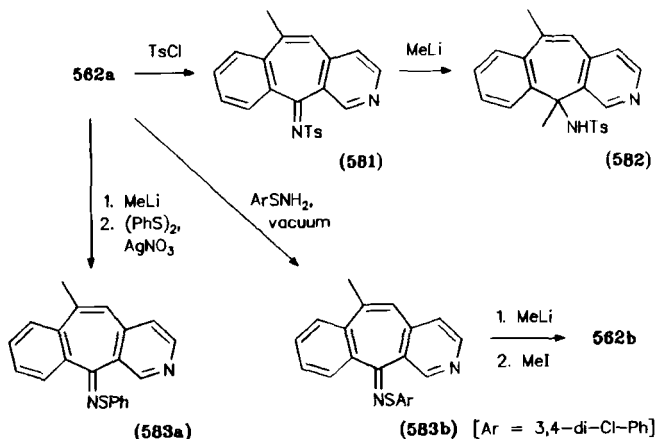


SCHEME 154

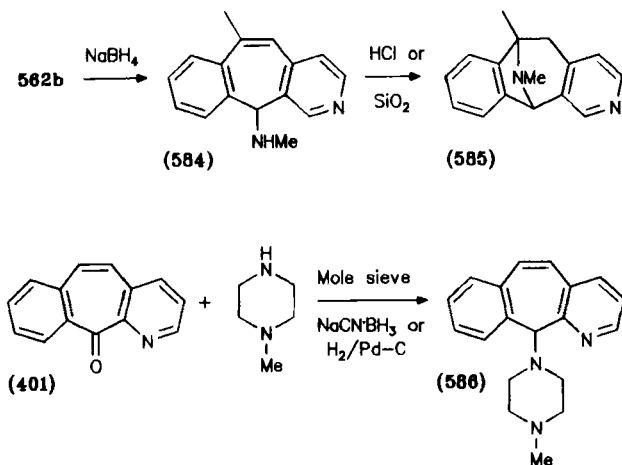
Among specific reactions of troponeimine derivatives, hydrolytic cleavage of oximes and hydrazones has already been described (Section II,A,1,d; Schemes 7, 150, and 152). Oxime **569** does not undergo cleavage or acetylation (83LA1845). Other oximes are smoothly esterified (53MI2; 58MI3; 59NKZ1175; 72AF133; 74JOC2956) and etherified (58MI2).

Pyrazolotroponehydrazones like **580a**, on treatment with carboxylic acid derivatives or aliphatic carbonyl compounds, are cyclized to fused [1,2,4]triazine derivatives (e.g., **580b,c**); with aromatic carbonyl compounds, they form azines (79BCJ1972; 80JHC1057, 80S331).

Tricyclic troponeimines like **562** offer a number of interesting reactions (Schemes 155 and 156). Sulfenylation can be accomplished by Davis'



SCHEME 155



SCHEME 156

method or by means of a suitable sulfenamide to give **583a** or **b**, respectively (85JHC805). Sulfenimine **583b** with methyllithium suffers nitrogen-sulfur bond cleavage and then, with methyl iodide, *N*-methylation (86JHC145). However, imine **562a**, after protection by the *N*-tosyl group (in **581**), can be *C*-methylated to give **582**.

Furthermore, imines like **562b** are smoothly reduced to afford amines (**584**) that, without being isolated, undergo transannular cyclization to give endimines like **585** (Scheme 156; 82JHC897, 82JHC967; 85JHC555). The products are comparable to hydroxyendimines (like **392**) obtained by the nonreductive synthetic variant (Section IV,A,4,c).

The sequence tropone (e.g., **391**) to imine to amine to endimine (e.g., **585**) can occur in a one-pot reaction (80SAP7807011). An example of a more direct reductive amination is the formation of piperazino derivative **586** from **401** (88WOP8803138).

## B. TROPYLIUM SALTS

### 1. General Remarks

As expected, the cationic tropylium ring proves to be inert toward electrophiles but reacts readily with nucleophiles. Whereas hardly any electrophilic reaction could be detected (73MI2, p. 1605), attack of nucleophiles leads to the most characteristic transformations of these cations [56AG661;

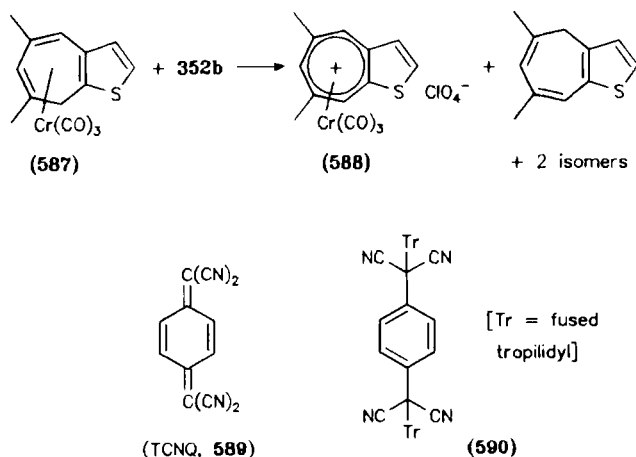
67UK1721; 72HOU(5/1d)301, p. 325; 73MI2, pp. 1603 and 1627; 74UK1739; 84MI2, p. 76; 85HOU(5/2c)49, p. 78]. The stabilities of fused tropylium systems toward solvolysis were discussed in Section III,B,3,b (cf. Table XXII).

Electron densities obtained from molecular orbital calculations on thieno- and pyrrolo-fused derivatives are listed in Table XXIII (Part B). Similar values were obtained with furo- and isoxazolotropylium salts **218**, **333**, and **329** (Section III,B,2,b). In the field of tricyclic compounds, electron densities of furothieno-fused (**237a**, **238a**) and bisthieno-fused ions (**237b**, **238b**; Scheme 57) were calculated (73ACS2257).

## 2. Complexation

a. *Metal  $\pi$ -Complexes.* Metal  $\pi$ -complexes of tropylium ions are well known (73CRV293, pp. 320 and 340). A practical synthetic method is that of hydride abstraction (Section II,C,1,a) from the corresponding tropylidene complex. In the case of complex **587** (Scheme 157), the usual reagents failed and the tropylium ligand itself (**352b**) had to be used to get tropylium complex **588** together with isomeric tropylidenes [71JOM(33)195]. This complex exhibits characteristic  $^1\text{H-NMR}$  shifts (Section III,B,2,a, penultimate paragraph) and UV bands [71CR(273)160].

b. *Charge-Transfer Complexes.* Early on, it was postulated that charge-transfer complexes of tropylium salts exist, for instance, in the case of the simple tropylium halides (67UK1721; 73MI2).



SCHEME 157

Certain benzazino- (**223**, **224**) and azolotropylium species (e.g., **640a,b**; Scheme 172) were found to form highly conductive salts with tetracyanoquinodimethane (TCNQ) **589** anion-radicals [88BCJ271; 94H(38)2691]. These reactions are controlled by the first reduction potentials  $E_1^{\text{red}}$  of the tropylium salts and yield the following products:

1. simple salts (1:1) from **223a-c** and **224a,c** ( $E_1^{\text{red}} < -0.43$  V);
2. complex salts (1:2) from 1:1 salts + TCNQ or from **224b**;
3. coupling products **590** from **216** ( $E_1^{\text{red}} > -0.2$  V).

Similarly, among thiazole derivatives only those (e.g., **640a,b**) having low reduction potentials (less than  $-0.34$  V) give CT complexes.

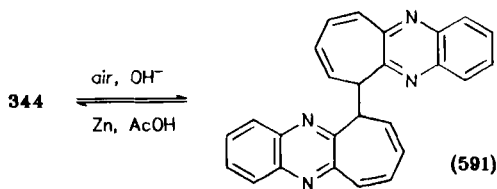
Electrical resistivities, especially of the 1:1 salt formed from **223b**, are relatively low. In contrast to the usual experience, however, the IR nitrile stretching frequencies of these salts are not linearly correlated with the degree of charge transfer.

### 3. Reactivity at the Seven-Membered Ring

a. *Oxidation.* Whereas monocyclic tropylium salts on oxidation usually undergo ring contraction, benzotropylium salts give benzotropones (84MI2, pp. 77 and 85, respectively). A third reaction is that undergone by the quinoxalotropylium ion **344** (= **252**). On air oxidation in the presence of alkali, it easily yields dimer **591** (Scheme 158), presumably by dimerization of a mesomeric radical (89BCJ1158). In the absence of air, deprotonation takes place (Section IV,B,4,b).

b. *Nucleophilic Reactions at Ring Atoms.* Nucleophiles, on reacting with monocyclic tropylium salts, suffer "tropylation" to give tropylienes substituted at C-7 (61MI1, p. 137). Benzotropylium salts are attacked at the 5- and/or 7-positions (84MI2, p. 84, 84MI3). Heterocyclic derivatives like thieno- or pyrrolotropylium salts have their most electrophilic sites at the 4-, 6-, and 8-positions (Table XXIII, Part B).

Earlier sections dealt with the different stabilities of tropylium salts against solvolysis (Section III,B,3,b), their disproportionation (Section



SCHEME 158

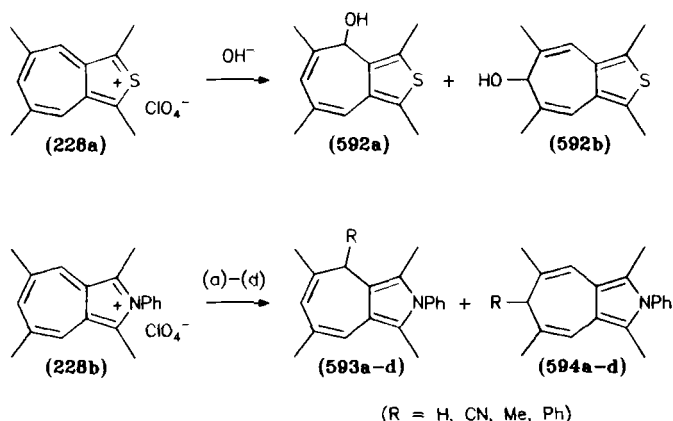
II,A,1,c), tautomerization (Section III,B,4), and application as hydride abstractors (Section II,C,1,a).

Thus, thieno[c]tropylium salts (like **228a**) are hydrolyzed even by 40% perchloric acid, and are rapidly decolorized by water, alcohols, amines, amides, and carbonyl compounds. The corresponding pyrroles (like **228b**) are more stable and are inert toward those reagents (68ZOR907).

In the rapid alkaline *hydrolysis* of thienotropylium salt **228a**, two isomeric carbinols (tropols), **592a** and **b** (Scheme 159), were detected (69ZOB2601). Likewise, tetracyclic pyrrole **335** on hydrolysis gives the tropol, whereas deprotonation (Section IV,B,4,b) occurs in the presence of anhydrous triethylamine (72CB1224). Another tropol, **597** (Scheme 160), is obtained from iron complex **285** (78AJC1607).

The addition of the hydride ion and of carbon nucleophiles was thoroughly investigated by El'tsov and co-workers (68ZOR1096; 69ZOR2072; 70ZOR2126). Again, tropylienes substituted at the 4- and 6-positions (e.g., **593** and **594**) were obtained.

The ratio of the *reduction* products (**593a**, **594a**) does not depend on the reducing agent ( $\text{LiAlH}_4$  or others) but differs according to temperature and solvent. A nonequilibrated mixture of isomers **593a** and **b** in acetonitrile does not change its composition unless tropylium salt **228b** is added. This



[ (a) =  $\text{LiAlH}_4$ , (b) = KCN, (c) =  $\text{MeMgI}$ , (d) =  $\text{PhMgBr}$  ]



SCHEME 159



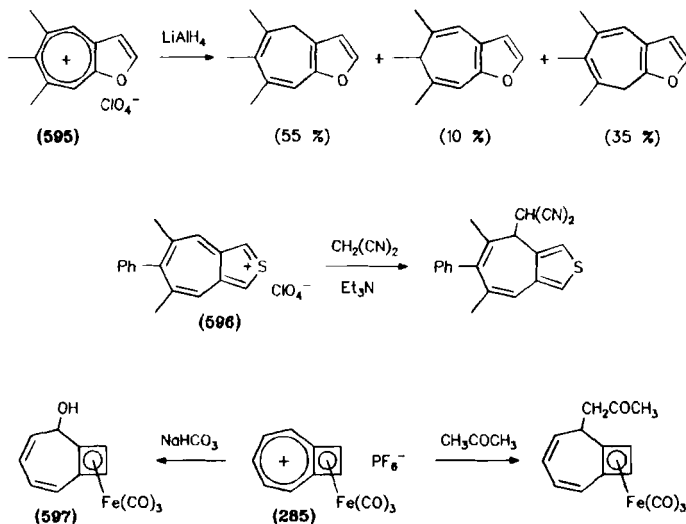
means that their isomerization takes place as a reversible hydride exchange between two tropylienes and the tropylium cation (Scheme 159); hence, the ratio of isomeric reduction products is thermodynamically controlled.

Kinetic control was observed when the reduction proceeded in a suspension or when the substrates contained a methyl or phenyl group at C-6 (68TL735, 68ZOR1096; 69ZOR1135). In these cases decreased solvation (favoring C-6) or steric hindrance (favoring C-4), respectively, led to a different product ratio.

Besides complex hydrides, other hydride-ion donors were used: 1,3-dimethyl-2-phenyl-, 1,3-dimethyl-5-nitro-, and 1,3-dimethylbenzimidazoline; 1,2-dimethyl-3-phenyl- and 1,2-dimethylindazoline; or suitable tropylienes.

As a rule, the analogous reduction of [c]- and [b]-fused species gives two or three isomeric tropylienes, respectively. Examples are those of furans like **595** [Scheme 160; 77BSF(2)75; 85MI1], thiophenes (71BSF1437; 81MI1), and isoxazoles like **329** (86CL1925). Electrochemical reduction of thieno[b]tropylium salts likewise yields three isomeric tropylienes [71CR(273)160; 80CJC263].

Unusual selectivity, however, is observed in the reduction (and Grignard reaction) of 6-phenyl- (e.g., **337a**) and 1,3-dibromothienc[c]tropylium salts which are exclusively attacked at C-4 or C-6, respectively (74YZ1452). In the tricyclic series, pyrrole **647** (Scheme 173) is reported to give a single reduction product [94JCS(P1)2579] whereas furoditropylium salt **260** forms



SCHEME 160

a mixture of furoditropylienes [85JCS(CC)1547]. 3-Acetylfurotropylium salt **333** is reduced to 3-(hydroxyethyl)furotropyliene (77BCJ3425).

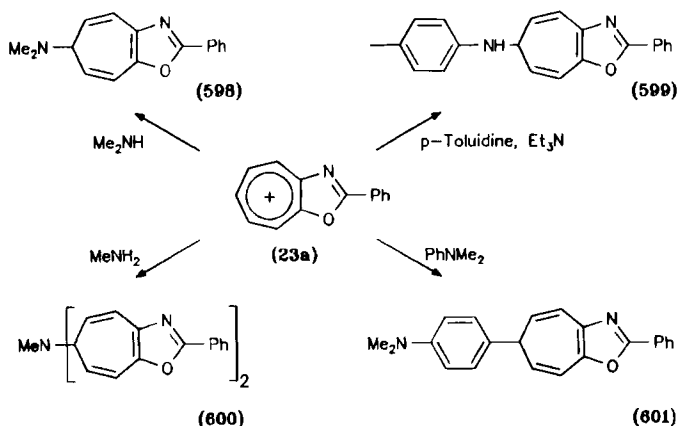
On catalytic hydrogenation, benzofurotropylium salts like **611** (Scheme 164) are transformed into cyclohepteno derivatives (e.g., **612**; 67BCJ1480).

Among *carbon nucleophiles*, cyanide and Grignard reagents again lead to isomeric products, such as **593b-d** and **594b-d** (Scheme 159). Malononitrile or acetone, however, attack thiophene **596** (74YZ1452) and iron complex **285** (78AJC1607), respectively, only in the  $\alpha$ -position (in relation to the bridgehead).

Imidazolium salt **343** adds malononitrile at C-6; after spontaneous dehydrogenation, imidazoheptafulvene is isolated (65CPB810). Likewise, dimethylaniline attacks oxazolotropylium salt **23a** (Scheme 161) preferentially at C-6 to give tropyliene **601** in addition to a small amount of the 4-substituted isomer (67CPB627).

According to Scheme 161, several *nitrogen nucleophiles* usually aminate fused tropylium salts at the 6-position to afford tropylienes of the types **598-600** (67CPB627; 70CPB581). Compound **598**, on standing in solution, undergoes rearrangement (slowly in carbon tetrachloride or benzene, but rapidly in methanol) to its isomers substituted at C-4 or C-8. The ratio of the isomers reaches an equilibrium (C-6:C-4:C-8  $\sim$  3:5:2), presumably by the intermolecular shift of the dimethylamino group via tropylium ion **23a** (73MI1, p. 222; cf. Scheme 159).

Toluidine derivative **599** does not show this rearrangement. Amination at C-6 is also observed with thiazol **23b**.



SCHEME 161

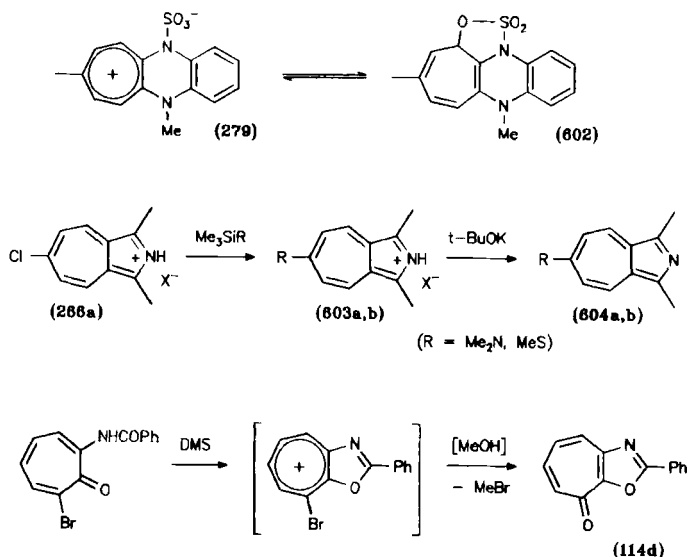
Along with the hydrolysis of tropylium salts (see above), the tautomerization of sulfonate **279** to give sultone **602** (Scheme 162) exemplifies the attack by an *oxygen nucleophile* (89BCJ1158).

c. *Reactivity of Nuclear Substituents.* *N*-Silylamines and *S*-silylmercaptans allow the chlorine in chlorotropylium salt **266a** to be substituted, a reaction which is not achieved by the use of free secondary amine. Amino and (not isolated) methylthio compounds **603a,b** are formed (84S119).

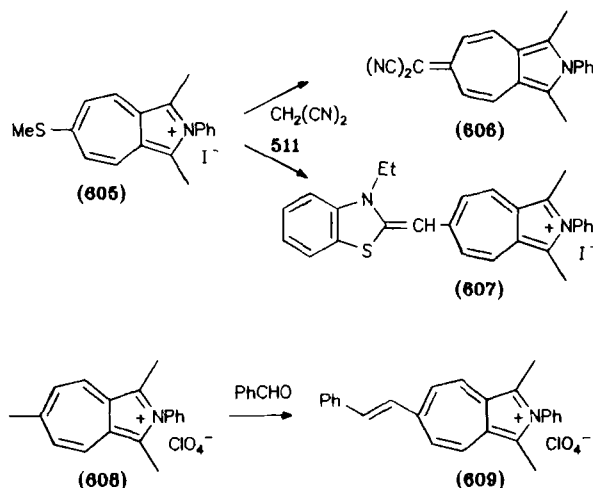
The synthesis of oxazolotropones **114d** or **24a** from bromotropone derivatives and dimethyl sulfate (Sections II,A,3,e and II,A,3,g, respectively) is explained by the reactivity of intermediate bromoxazolotropylum ion with methanol; indeed, methyl bromide was detected in this reaction (Scheme 162; 67CPB619).

Suitably substituted tropylium salts offer an alternative to condensation with active methylene compounds (cf. Section IV,A,4,c) even if the application of tropones fails. Thus, 6-chloro derivative **266c** (82CB3756) or thioether **605** (Scheme 163; 91KGS1432) were used to get, respectively, sesquifulvalenes and heptafulvene **606**. *O*-Functionalized compounds are likewise applicable (Scheme 110; cf. 73CRV293, p. 308).

The condensation of thioether **605** and benzothiazolium salt **511** affords cyanine dye **607**. This *monomethinecyanine* ( $\lambda_{\max}$  553 nm) absorbs at nearly as high a wavelength as the symmetrical *thiatri*methinecyanine (cf. 94KGS193).



SCHEME 162



SCHEME 163

The 6-methyl group in pyrrolotropylum salt **608** readily reacts with aromatic aldehydes to give styryl dyes like **609** (69ZOR2242) and other dyes (94KGS193). A methyl group in the 1- and 3-positions is unreactive. One additional methyl group at C-5 lowers the yield, while two methyl groups at C-5 and C-7 prevent the reaction because of steric hindrance.

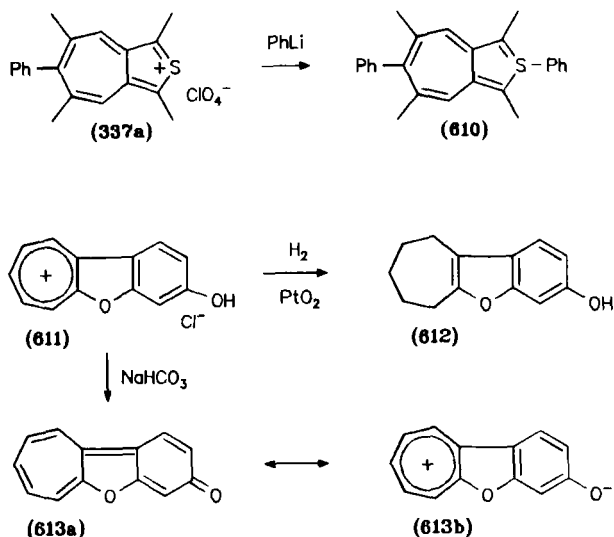
Hydroxytropylum salt **233** (74YZ1429), in a reversal of its formation, is hydrolyzed to the tropone.

#### 4. Reactivity at the Heterocyclic Ring

a. *Electrophilic Substitution.* In bicyclic tropylium systems, the 1- and 3-positions appear to be prone to electrophilic substitution (cf. Section IV.A,5,c). Bisheterocyclotropylum salts **237b** and **238a,b** (73ACS2257), with concentrated deuteriosulfuric acid, smoothly undergo deuterium exchange in the heterocyclic  $\beta$ -positions. This is in agreement with NMR-spectroscopic results and MO calculations; furthermore, it was proved by the synthesis of authentic 3-deutero derivatives.

b. *Nucleophilic Reactions.* Thienotropylum salts like **337a** (Scheme 164; 74YZ1452) on *S*-arylation give thiaazulenes (e.g., **610**) comparable to "thiabenzene" [84CHEC(3)925].

Deprotonation by alkali or amines to azaazulenes is commonly observed with *N*-protonated pyrrolotropylum salts, often reversing their formation. Examples are those of bicyclic species like **603** (to give **604**, Scheme 162;



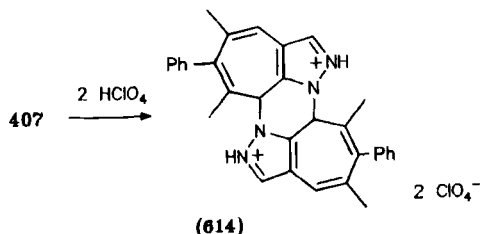
SCHEME 164

79CB2087; 84S119), tricyclic compounds like **263** (to recover **262**, Scheme 66; 75TL1849) or **648** [to give **644**, Scheme 173; 94JCS(P1)2579], and tetra- or pentacyclic pyrroles like **641** [Scheme 172; 94JCS(P1)2721]. Similar reactions proceed with diazepine **345** (81JHC335) and with benzazines, for example, **344** (89BCJ1158, 89BCJ2307).

Benzofurotropylium salts (cf. Section II,C,3,a) that bear a hydroxyl group at C-3 (e.g., **611**) are deprotonated to yield mesomeric “furo-*p*-benzoquinonetropides” or “tropyliene quinones” like **613** [67BCJ1480; 71JCS(P1)2399].

### 5. Cyclization Reactions

In addition to cyclocondensations onto benzazinotropylium systems (Section II,D,2), dimerized pyrazolotropylium salt **614** (Scheme 165) should be



SCHEME 165

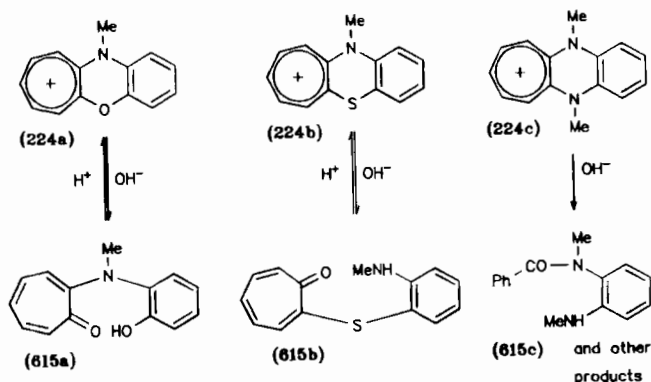
mentioned [72JCS(P1)1623]. Presumably, **614** is formed from the intermediate monomeric tropylium salt. Deprotonation gives the dimeric base.

## 6. Ring Cleavage and Transformation

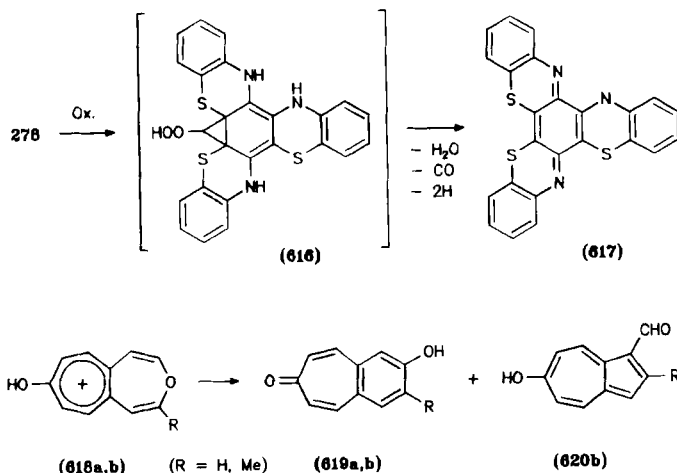
a. *Cleavage of the Heterocyclic Ring.* In the series of 11-methylbenzazinetropylium ions **224a–c** (Scheme 166), a comparison between the reactivities reveals different routes of alkaline ring cleavage (85BCJ165; 89BCJ1158). Tropones **615a** and **b** result from the attack of hydroxide ion onto C-5a or C-10a, respectively. Amide **615c** is one of the products of ring contraction (Section IV,B,6,c).

b. *Exchange of the Heterocyclic Ring.* Such exchange easily occurs in the azolo- and benzazinetropylium series. Under the influence of *p*-toluidine, oxazotropylium salts **23a** are transformed to imidazotropyliene **25c** and the corresponding troponeanil (67CPB627). The same products are directly obtained on the disproportionation of imidazotropylium salt **23c**. The conversion of bis(benzazino)tropylium salt **272** to **273** is shown in Scheme 68 (Section II,D,2; 88CL1593).

c. *Ring Contraction.* Ring contraction of the tropylium ring is effected by most oxidizing agents and is again believed to pass through norcaradiene-type intermediates (66MI2, p. 106). A mechanistic relative of the reaction of benzazinetropone **552** (giving **554**, Scheme 146; Section IV,A,7,d) is the transformation of tris(benzazino)tropylium salt **278** into *p*-benzoquinonediimide-type derivative **617** [Scheme 167; 89H(29)1459]. This oxidative degradation of **278** is assumed to proceed via peroxidation at C-6, tautomerization



SCHEME 166



SCHEME 167

(to norcaradiene **616**), dehydration, decarbonylation, and dehydrogenation.

Contraction of the heterocyclic ring is reported to occur in the oxepinotroplium series (**618** or **346a**). These cations, once formed from oxepinotropones (e.g., **156a**) in trifluoroacetic acid solution (Section II,C,1,d), suffer rapid rearrangement in a few hours (**618a,b**) or even in a few minutes (phenyl derivatives). Obviously, hydroxybenzotropones **619** and hydroxyazulenes like **620b** are obtained via benzene oxide intermediates (88CL1647; 92TL6487).

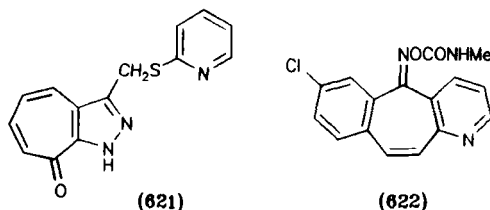
## V. Applications

### A. PHARMACEUTICAL USES

The troponoid system is included in many natural products, including alkaloids and antibiotics. Therefore, its discovery attracted immediate pharmacological interest.

Among heterocyclic derivatives, pyrrolotropones (which are structurally similar to indoles), tricyclic thieno- or pyrrolobenzotropones, and other compounds have been claimed in patent applications. Table XXVI lists relevant effects and structures (cf. Scheme 168).

Other troponoids, such as tricyclic thiophenes **473** and **398b**, are synthetic precursors of potential drugs (66HCA214; 90HCA1197). With regard to



SCHEME 168

tricyclic pyrrole **497b** (Table XXVI), “pro-drugs” bearing acetonyl or 2-acyloxypropyl groups in the 2-position have been claimed. These groups are thought to be metabolized *in vivo* to give the carboxymethyl group of **497b**.

In pharmacodynamic studies, the effects of troponoids on enzymatic processes were examined *in vitro* (in mouse and rat liver). Triazolotropone **439** stimulates the metabolism of ribonucleic acid (56MI5); it inhibits the glycolytic (energy-yielding) system (60MI2), but shows only slight inhibitory activity on monoamine oxidase (88YZ754). Pyrrolotropolone **179b** does not inhibit catechol-*O*-methyl transferase (66MI1).

## B. PHOTOGRAPHIC USES

### 1. Electrophotography

In numerous patents the synthesis of suitable furo-, thieno-, and pyrrolo-tropylium salts is described, for example, that of squarylium dyes like **623** and **624** (Scheme 169; 85JAP60/262163; 86JAP61/185487; 88JAP63/41858, 88JAP63/102990). These substances serve as components of photoconductive thin layers for electrophotographic photoreceptors. The materials are claimed to exhibit increased sensitivity, stability on storage, and durability to laser-beam reading.

### 2. Silver Halide Photography

Dyes having similar constitutions (e.g., **625**) are claimed to improve spectral sensitivity in classical photography (88JAP63/110444). Other cyanine dyes (**509**, **512**, **607**) have already been described (Sections IV,A,5,e; IV,A,5,f; IV,B,3,c). It has also been reported that fused tropylium salts such as **224**-type compounds stabilize photographic emulsions (90JAP02/156240).

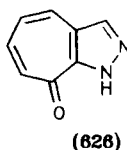
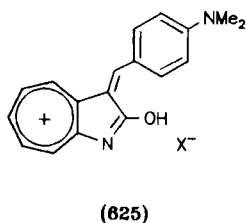
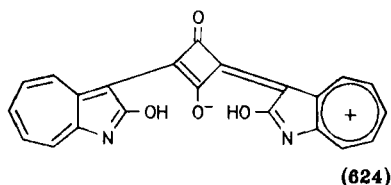
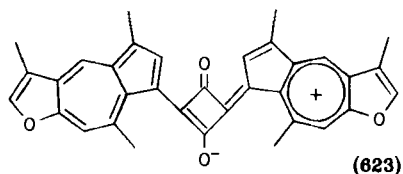


TABLE XXVI  
PHARMACOLOGICAL ACTIVITY OF TROPONIDS WITH FUSED HETEROCYCLIC RINGS

Activity	Fused <sup>a</sup> heterocycle	Characteristic substitution and further fusion <sup>b</sup>	Typical structure		Reference
			Formula	Scheme	
Analgesic	pyrrole <sup>d</sup>	—	<b>101a</b>	24	69MI1, 69MI2
	pyrazole <sup>c</sup>	—	<b>81</b>	20	63JAP4081
Antiphlogistic	thiophene	5,6-benzo-2-carb(alk)oxymethyl	<b>477</b>	126	73GEP2316844
		5,6-benzo-2-carb(alk)oxyacyl	—	—	75GEP2441592
	indole <sup>c</sup>	—	<b>177</b>	42	67JAP13101
	imidazole, oxazole	2-phenyl	<b>24a,c</b>	6	68JAP26504
Analgesic and antiphlogistic	pyrrole	1-benzyl	<b>431b</b>	116	65JAP6228
		1,3-dibenzyl	<b>437b</b>	118	64JAP28764
		6,7-benzo-2-carboxymethyl	<b>497b</b>	131	81EUP24807
		6,7-thieno-2-carboxymethyl	—	—	81EUP35853
		2-phenyl	<b>190</b>	46	64JAP4482
	thiazole	2-phenyl	<b>190</b>	46	64JAP4482

Antitubercular	thiazole <sup>c</sup>	2-amino	<b>480</b>	127	64JAP10132
		2-mercapto	<b>197</b>	47	64JAP10133
Antiulcer	pyrazole <sup>e</sup>	3-(heterocyclylthiomethyl)	<b>621</b>	168	91JAP03/74367 <sup>g</sup>
Antibiotic	oxathiol	("thiotropocin")	<b>168</b>	40	84MI1
	pyran <sup>c</sup>	("antibiotic C")	—	—	83BRP2113672
Antihypertensive	pyrrole	3-alkyl	<b>359a</b>	96	62JAP12689
	indole	benzo <sup>h</sup>	—	—	68USP3393208
	imidazole <sup>f</sup>	1-(biphenylmethyl)	<b>432a</b>	117	91EUP432737 <sup>i</sup>
			<b>432c</b>	117	93GEP4316117
	pyridone <sup>f</sup>	6,7- or 7,8-benzo	<b>447</b>	120	87USP4639457
Antiarrhythmic	thiophene	8-(aminoalkoxy)-5,6-benzo	( <b>9</b> )	3	77GEP2625642
Antidiabetic	pyridone	3-carboxy-1-carboxymethyl	—	—	83USP4381304
			—	—	83USP4382088
Antiallergic	pyridone	2-carb(alk)oxy	—	—	78USP4130649
Antiserotonin	pyrrole	3-(aminoethyl)	<b>179a,b</b>	43	64NEP6406914
Depressant	pyridine	5-(acyloximino)-6,7-benzo	<b>622</b>	168	72AF133

<sup>a</sup> Rings with one heteroatom are [b]-fused unless otherwise stated. <sup>b</sup> The numbering used is that of bicyclic systems (**295**, **296**). <sup>c</sup> Tropolones. <sup>d, e, f</sup> Also antistrychnine, antiallergic, or cardiovascular agents, respectively. <sup>g</sup> See 90H(31)677; 94JHC1557. <sup>h</sup> 6*H*-Benzo[5,6]cyclohept[1,2,3-*cd*]indoline-1,6-diones. <sup>i</sup> See 91MI1.



SCHEME 169

### C. OTHER USES

In the field of plant biochemistry, pyrazolotropone **626** exhibits toxic effects on the mitotic cell (62MI2).

Thienobenzotropones like **473** are claimed as polymerization inhibitors in plastics technology, as antioxidants, and as insecticides or fungicides (65NEP6414549). Tetracyclic pyrrolotropones are used as ultraviolet screens (68USP3393208). Finally, benzopyrazinotropylum salt **224c** and related compounds are declared to be electrical conductors (89JAP01/211572).

## VI. Addendum to Part 1, Section II: Recent Synthetic Work

### A. TROPONES AND TROPOLONES

#### *To Section II,A,I,b*

Cycloheptapyrrolotropones **645** and **646** (see Scheme 173) are obtained, along with azaazulene **644**, on oxidizing dihydro derivative **642** [94JCS(P1)2579].

Pentacyclic furotropyliidenes, on oxidation, give 12-oxo compounds (96T1707), i.e., isomers of known 14-oxo derivatives (e.g., **53a**, Scheme 13).

*To Section II,A,2,c*

Spiropyrazoline **627** (or the nitro-free analog) disproportionates to give hydrazone **628** and pyrazolotropone **294a** (Scheme 170; 93MI2; 94TH1). Homologs that are alkylated in the dienone ring do not give any tropone.

*To Sections II,A,3,a,d, and k*

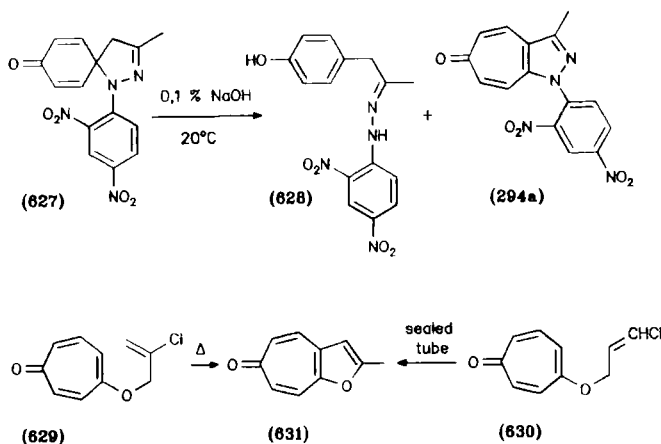
Another Claisen rearrangement leads from  $\gamma$ -tropolone 2-chloroallyl ether **629** to furotropone **631** [93H(36)1725; 94MI2]. The same product can be obtained from the corresponding diastereomeric 3-chloroallyl ethers **630** when oxygen is excluded (94BCJ2803).

In an "open vessel,"  $\gamma$ -tropolone allyl ether (**632**) predominantly gives allyltropolone **633** (and, by dehydrogenation, traces of **634** and **635**); **633**, however, affords **634** and **635** as the main products (Scheme 171). Pyran **634** suffers autoxidation (Section IV,A,4,a). On oxidation by CAN,  $\gamma$ -tropolone and allyl derivative **633** dimerize to ditroponofurans **637** and **635**, respectively.

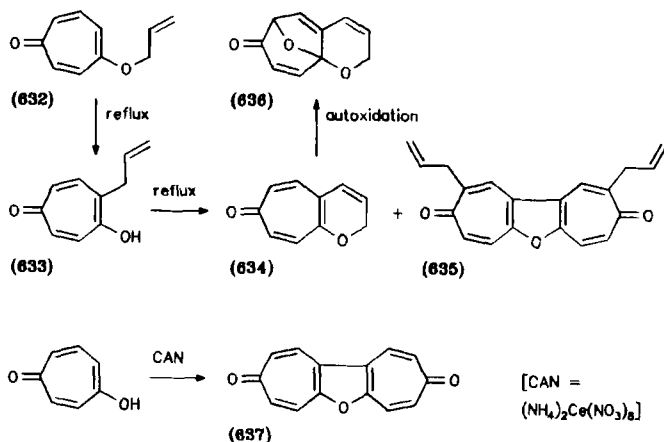
The reactions show that  $\gamma$ -tropolones are much more reactive with radical species than  $\alpha$ -tropolones; thus they suffer attack at the 1-, 5-, and 7-positions that result in dimeric products, among others.

*To Sections II,A,3,b and c*

In analogy to tropones **7b**, **79a,b**, **90**, and **621**, respectively, the following compounds were synthesized from 3-cinnamoyl- or 3-acetyltropolone derivatives:



SCHEME 170



SCHEME 171

1. Pyronotropones (95MI4);
2. 3-styrylisoxazo- and -pyrazolotropones substituted at the phenyl group (95MI1, 95MI3);
3. the 5-nitro derivative of isoxazolotropone **90** (95MI2);
4. 3-(benzimidazolylthiomethyl)-1-methylpyrazolotropones and, as by-products, 3-hydrazinomethyl derivatives (94JHC1557).

### To Section II,A,3,h

A new diene reaction of dehydrotropone (**146a**) is depicted in Scheme 172. Addition of 4-phenyloxazoles leads to nonisolated adducts like **638** that, after facile loss of benzonitrile by a retro-Diels–Alder reaction, gives furotropone **307a** (94TL8421).

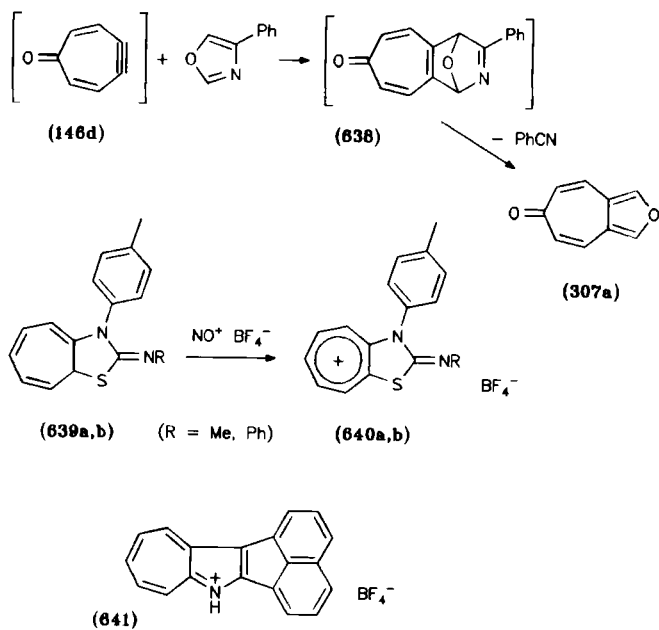
## B. TROPYLIUM SALTS

### To Section II,C,1,a

Abstraction of hydride ions from tropylienes by nitrosyl or trityl tetrafluoroborates leads to 2-imino-3-arylthiazolotropylum salts like **640a,b** [94H(38)2691] and to cycloheptaazaazulenium salt **643** or (unstable) 14- $\pi$ -electronic pyrrolotropylum salt **647** [Scheme 173; 94JCS(P1)2579].

### To Section II,C,1,b

The formation of azaazulenium or pyrrolotropylum salts by protonation of azaazulenes is exemplified by the acenaphtho-fused com-



SCHEME 172

pound **641** [94JCS(P1)2721] and cyclohepta-fused systems [Scheme 173; 94JCS(P1)2579].

Thus, tropylidene **644** and tropones **645** and **646** are converted into *N*-protonated or *N*-methylated species **648**–**650**; tropone **646** can even be bis-protonated at the nitrogen to give **651**.

### To Section II,D,2.

Nozoe, in his scientific autobiography (91MI3), gives another survey of trobenzazine chemistry.

## ACKNOWLEDGMENTS

The author is grateful to his colleagues, Dr. Horst Engelmann (Wolfen), Dr. Achim Hantschmann, Prof. Dr. Erich Kleinpeter, and Prof. Dr. Horst Wilde (Leipzig), for valuable discussions.



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